VOLUME 12
NUMBER 5
MAY, 1959

ORAL SURGERY
ORAL MEDICINE
and ORAL PATHOLOGY

OPERATIVE ORAL SURGERY

SURGICAL OPERATIONS ON THE ALVEOLAR RIDGE TO CORRECT OCCLUSAL ABNORMALITIES

Heinrich Köle, M.D., Graz, Austria

(Continued from the April issue, page 420)

SURGICAL PROCEDURES TO FACILITATE SUBSEQUENT ORTHODONTIC TREATMENT

SURGICAL intervention on the alveolar ridge which may facilitate subsequent orthodontic treatment will be described next. There exists an entire group of tooth and alveolar malpositions which cannot be corrected by surgery alone, while orthodontic correction alone would take years. Such prolonged orthodontic treatment may involve a financial commitment which the patient cannot afford, and the treatment results are unpredictable since the behavior of bone malleability may cause failure or only relative success. We may presume that the cause of this is to be found in the deficiency of the reconstructive vitality of the tissues. A relapse may even occur after long years of treatment. Bichlmayer,[4-7] Skogsborg,[26] and Ascher[1, 2] have pointed out these difficulties of moving and retaining the teeth in the desired position. Their experience, however, is based only on the surgical and orthodontic treatment of protrusion (Fig. 25).

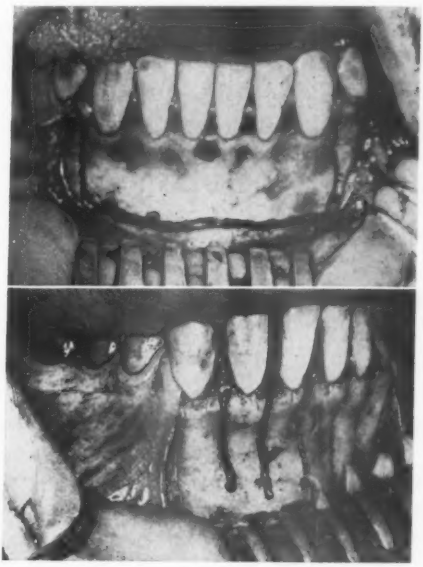
Corticotomy.—Practical experience has shown that we may achieve a quicker movement of the teeth when a corticotomy has been performed, since the main resistance to movement is encountered in the cortical layer. Probably the organism needs a longer time to rebuild the thick cortical bone than the thin trabecula of the spongiosa.

Because of these considerations, I do osteotomies on the cortical layer at different points to facilitate orthodontic treatment and prevent a relapse. The corticotomy can be performed for a single tooth or for a group of teeth.

From Graz University Dental Clinic, Department of Maxillo-Facial Surgery (Prof. R. Trauner, Director).

The teeth are then moved in a short period and are generally not loosened, as when strong forces are applied to them. The principles of corticotomy are as follows. In order to move a group of teeth, with their alveolar process, by orthodontic means, the cortical layer is osteotomized both buccally and lingually in its entire alveolar height. The spongiosa is left intact, serving as a nutritive pedicle to the bone denuded of its mucoperiosteum. This prevents injury of the alveoli. In addition, the bone is generally osteotomized horizontally well above the apices of the teeth (Fig. 26).

Fig. 26.



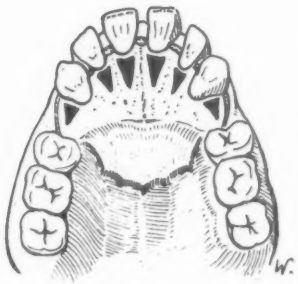


Fig. 25.

Fig. 27.

Fig. 25.—Bichlmayr's technique for corticotomy in cases with maxillary protrusion.
Fig. 26.—Corticotomy for orthodontic movement of teeth with alveolar ridge in case of alveolomandibular retrusion. Photograph taken during operation.
Fig. 27.—Corticotomy for orthodontic movement of single teeth in case of mandibular protrusion with diastemas between the teeth. Photograph taken during operation.

For the orthodontic movement of single teeth in malposition, the cortical layer is osteotomized only interdentally on the buccal and lingual sides (Fig. 27).

The advantages of the corticotomy are many. Osteotomy of the cortical layer only, leaving the spongiosa intact, prevents injury of the periodontium and pocket formation. It also prevents the devitalizing of a single tooth or of a group of teeth. The nutritive function of the bone to be displaced is maintained through the spongiosa, although the bone was exposed. Osteotomy of the cortical layer and subsequent healing should prevent a relapse. Not the least important feature is the fact that active orthodontic treatment is limited to a period of six to twelve weeks.

Roentgenographic control examination of teeth has never shown a root resorption. This is evident from the fact that it is not the tooth proper that is displaced but the tooth with its alveolar process. Vitality tests taken six months later have always been positive. Pocket formation on teeth whose cortical layer has been subjected to osteotomy has never been observed. The merits of the method have well established it as a supporting intervention which shortens an otherwise lengthy period of orthodontic treatment and which may be used in adults.

The following are surgical procedures to be used for various anomalies. The postoperative orthodontic treatment, its application, and its duration will be discussed only briefly.

Deep Overbite in Postadolescent Age.—The correction of deep overbite is extremely difficult. Yet, it is imperative, for this condition favors periodontoclasia and does not permit the elimination of the mandibular distoclusion. Abnormal facial features, such as the deep labiomental crease, may be eliminated at the same time. The following procedures are available.

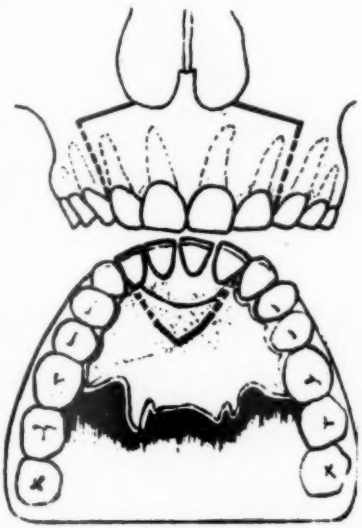
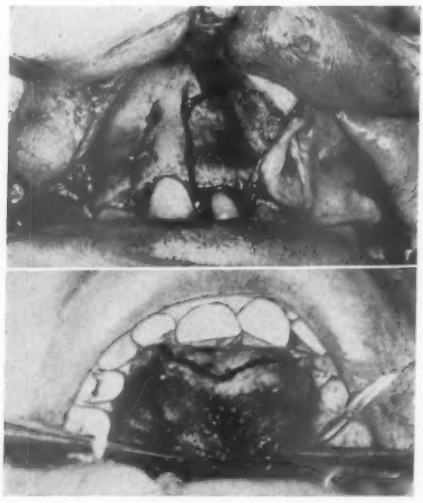


Fig. 28.—Sketch of the operative technique to advance the anterior maxillary teeth. The hatched line interdentally represents the corticotomy, and (also in the following sketches) the drawn line indicates the osteotomy.

Labioversion of the upper incisors (Fig. 28): For the correction of this condition, a vertical mucoperiosteal incision is made in the vestibule, one tooth's width distal to the proposed osteotomy. Usually it is between the central incisor and the lateral incisor, between the lateral incisor and the cuspid, or, rarely, distal to the cuspid. The bone is now exposed up to the anterior bony aperture of the nose. The interdental osteotomy is performed

with fine round burrs and fissure burrs. The cuts should be perpendicular and should not injure the alveoli. Only the cortical layer must be cut. The entire height of the alveolar bone to 1 cm. above the apical line is thus corticotomized. Thence, as far as the anterior bony aperture of the nose, the bone is cut throughout with fine osteotomes (Fig. 29, *A*). The palatal bone is then exposed, and the vertical cut is repeated as on the vestibular side.

A.



B.

Fig. 29.—Operation showing corticotomy on buccal (*A*) and palatal (*B*) sides in cases of deep overbite.

Fig. 30.—Orthodontic appliance with sagittal screw.

The bone on the palatal vault is cut to the nasal floor joining both the palatal vertical cuts, and a V-shaped edge is removed (Fig. 29, *B*). All mucosal incisions are sutured. Eight days later the orthodontic appliance with an extension screw for sagittal movement is inserted (Fig. 30).

It is also possible to use here an Angle appliance. The screw is activated twice during the first week and later only once a week. The movement of the teeth is therefore 0.5 mm. and later 0.25 mm. weekly. The appliance must be

worn continuously by day as well as by night, and it should be removed only for cleaning purposes. It is possible to cement the appliance into place for several weeks, as is done in palatorrhapheal rupture. The mucosal inflammation subsides quickly without any complication. The teeth reach the desired position in approximately eight to ten weeks (Fig. 31, *A* and *B*). As soon as the appliance is removed, a retention appliance is worn for six to eight months to permit complete consolidation of bone.

A.

B.

Fig. 31.

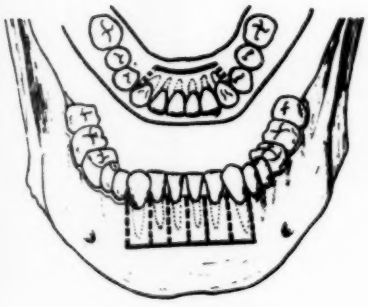


Fig. 32.

Fig. 31.—Deep overbite. *A*, Preoperative occlusion. *B*, Postoperative occlusion.
Fig. 32.—Sketch of corticotomy for advancing the lower front teeth.

Protruding of the lower anterior teeth: This procedure is indicated in most of these cases. It should be determined whether there is a mandibular or an alveolomandibular retrusion. In the latter a corticotomy is performed bucally, between the lateral incisor and the cuspid or between the cuspid and the first premolar. Lingually, the mucoperiosteum is undermined and a vertical bone cut is made with the Lindemann spiral crosscut burr mounted on an angle handpiece. The horizontal osteotomy is made 1 cm. below the apices. This cut also is made first with burrs and then completed with osteotomes through the entire thickness, including the lingual cortical layer. If simultaneous rotation of a single tooth or of all the teeth is desired, the corresponding corticotomy is performed in the bucal interdental spaces (Fig. 32). The subsequent orthodontic treatment is similar to that for the maxilla, but it takes approximately ten to twelve weeks to achieve the labioversion (Fig. 33).

The retention appliance is worn for one year. The labioversion of both cuspids causes a lateral open-bite. The posterior teeth elongate relatively

Fig. 33.—Orthodontic appliance with sagittal screw for advancing the mandibular front teeth.

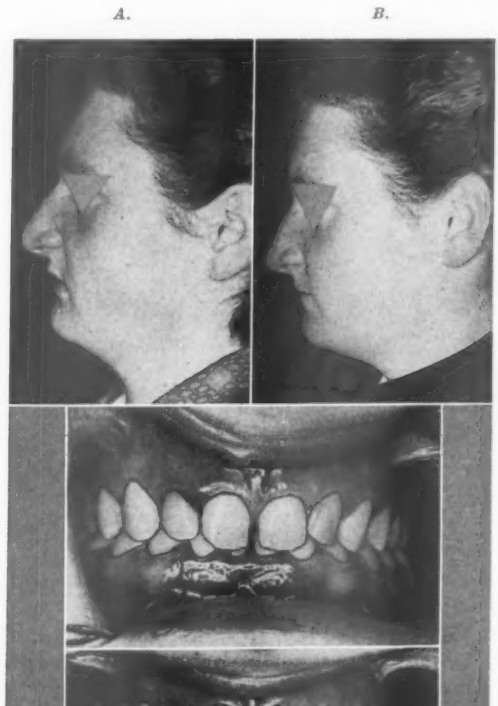
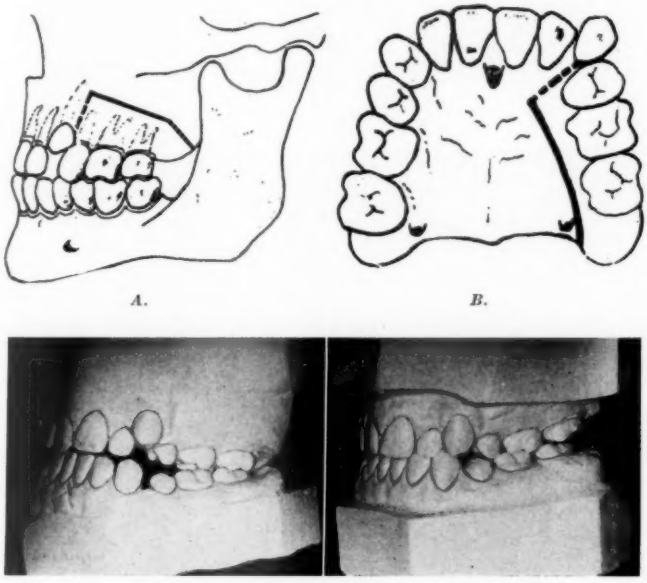


Fig. 34.—Case showing a deep overbite and a deep bite, before (*A*) and after (*B*) treatment. After elimination of the deep bite, an elongation of the lower facial third is achieved. *C*, Preoperative occlusion. *D*, Occlusion after protruding the maxillary and mandibular front teeth.

quickly and close the open-bite posteriorly. This eliminates the deep bite in the front (Fig. 34, *C* and *D*). The correction of the low bite produces an elongation of the lower facial third, and the labioversion of the lower front teeth corrects the pronounced labiomental crease (Fig. 34, *A* and *B*).

Distal Displacement of a Single Tooth or of a Group of Teeth.—Correction necessitates a long period of treatment in adult patients. It is especially difficult to create a space for the maxillary cuspid through distal displacement of posterior teeth if the second molars have already erupted. Surgical intervention is indicated when a gap of an extracted first premolar has been closed by the median migration of the upper second premolar and first and second molars and the canine is in a vestibular high position (Fig. 35, *A*, *B*, *C*, and *D*).



A. *B.*

C. *D.*

Fig. 35.—Case showing the canine in a vestibular high position. The premolar has been extracted. *A* and *B*, Sketch of corticotomy. *C* and *D*, Models before and after treatment.

The malposition of a completely erupted canine, with protrusion, vestibular high position, or crowding of the anterior teeth, can be corrected in a short time. The first premolar is extracted, and a V-shaped wedge is then removed from the alveolar process both vestibularly and palatally. A corticotomy is performed on the mesial vestibular and palatal side of the canine. Corticotomy of the bone on the opposite direction to the thrust is as important as removal of bone on this side of the thrust (Fig. 36). The subsequent orthodontic treatment takes two to three months. The appliance has a lateral extension screw and interdental spikes.

The distal displacement of the posterior mandibular teeth, by orthodontic means alone, is more difficult than that of the maxillary teeth. When a malpositioned mandibular cuspid is to be brought into alignment, the supporting corticotomy and first premolar extraction save more time than in the case of the maxilla (Fig. 37).

A. *B.*

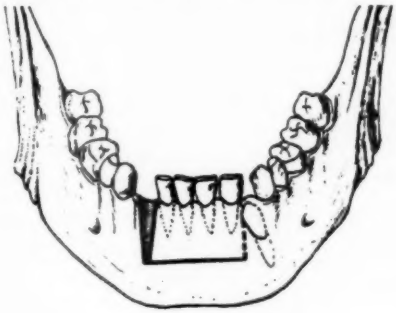
C. *D.* *E.*

Fig. 36.—Vestibular high position of the canine and early loss of $\underline{|5,\ 6}$ (35 years old). *A* and *B*, Sketch of corticotomy for distal migration of the first premolar. *C*, Occlusion before treatment. *D*, Occlusion two months after treatment. *E*, Occlusion nine months after treatment.

Fig. 37.—Sketch of corticotomy for distal movement of the canine in case of mandibular crowding.

The retrusion of all six lower front teeth after lingual and buccal corticotomy and premolar extraction is rarely indicated. It is performed only when there is a strong crowding of the teeth. The procedure for the lateral displacement of lower teeth is analogous to that for the maxillary teeth (Fig. 38).

Alignment of Rotated Teeth.—Teeth in rotation are aligned for cosmetic reasons only in the front. Premolars are aligned only in rare cases. The treatment of pronounced rotation can be accomplished by activating forces (elastics). To save time, a corticotomy is performed on both sides of the



A.

B.

C.

Fig. 38.—Retained mandibular canines—the right canine in an oblique position and the left canine in correct position but with no space for eruption. Correction involved extraction of $\overline{3}|$, corticotomy, and orthodontic treatment. *A*, Sketch of corticotomy. *B*, Before treatment. *C*, After six months' treatment.

tooth, buccally as well as lingually. The correct occlusion is usually attained in six to eight weeks. This procedure probably spares the periodontium more than do mere orthodontic measures.

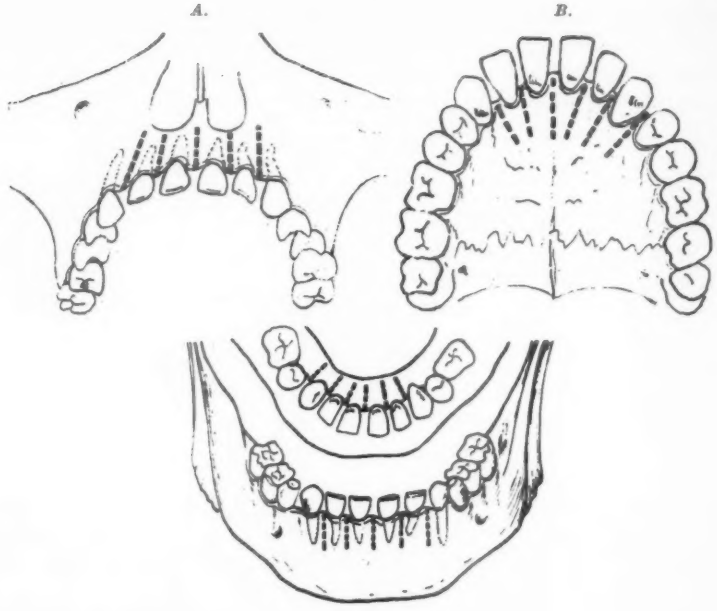


Fig. 39.—Case showing a protrusion with maxillary and mandibular diastemas. Sketch of corticotomy in the maxilla (*A* and *B*) and in the mandible (*C*). Occlusion before (*D*) and after (*E*) treament.

Correction of Spaced Teeth.—I have already dealt with crowded teeth. In maxillary and mandibular protrusion with diastemas between the teeth, the corticotomy is performed on the buccal and lingual as well as on the mesial and distal aspects of each tooth (Fig. 39). The bone is not completely osteotomized as recommended by Skogsborg,[26] and Ascher.[1-2] The mucoperiosteal incision is made along the gingival margin and the bone is exposed.

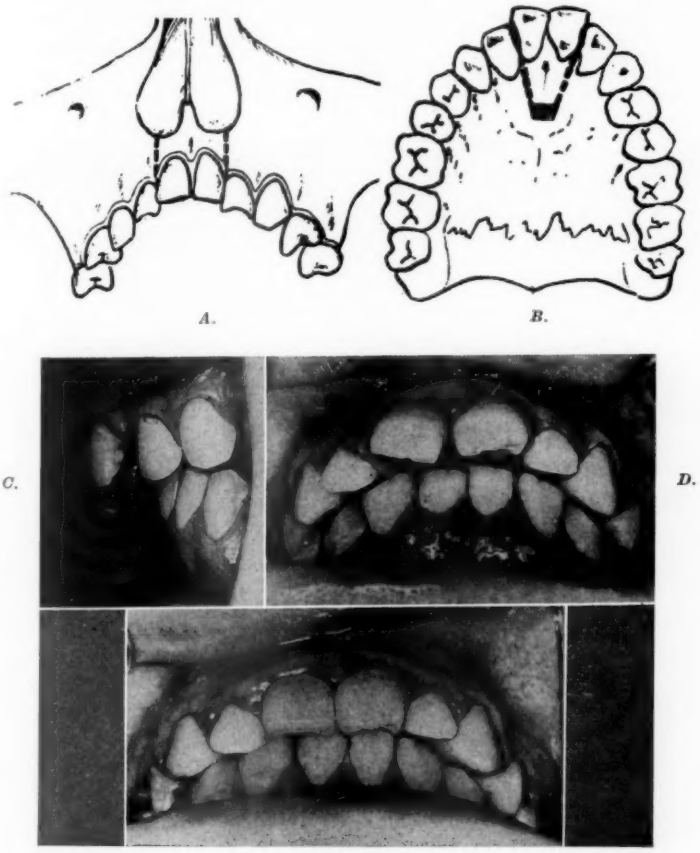


Fig. 40.—Protrusion of the two median maxillary front teeth. *A* and *B*, Sketch of corticotomy. *C* and *D*, Pretreatment occlusion. *E*, Occlusion after treatment.

The incisive artery should be spared. It can be drawn out a little to facilitate the corticotomy. If only the central incisors are protruding and there is space enough for their retrusion, the procedure is analogous to the surgical correction of deep overbite. The spongiosa of the bone serves here as a nutritive pedicle. On the palatal side a V-shaped wedge is removed (Fig. 40). The teeth are brought into the desired position in approximately ten weeks with a vestibular arch.

Linguoversion of Posterior Teeth With Compression of Alveolar Process.—Very good results are obtained with corticotomy for the correction of linguoversion of the mandibular teeth. After a palatorrhapheal rupture treatment, this mandibular anomaly should be eliminated immediately. Only the vetibular cortical layer is exposed. A corticotomy is performed between the teeth to be displaced. I use a circular saw to cut the corticalis. The subsequent orthodontic treatment is done with an extension-screw appliance used for six to eight weeks. The retention apparatus should be kept for approximately six months. If the compact cortical layer is thick, a horizontal strip is removed with the aid of osteotomes below the alveolar ridge (Fig. 41).

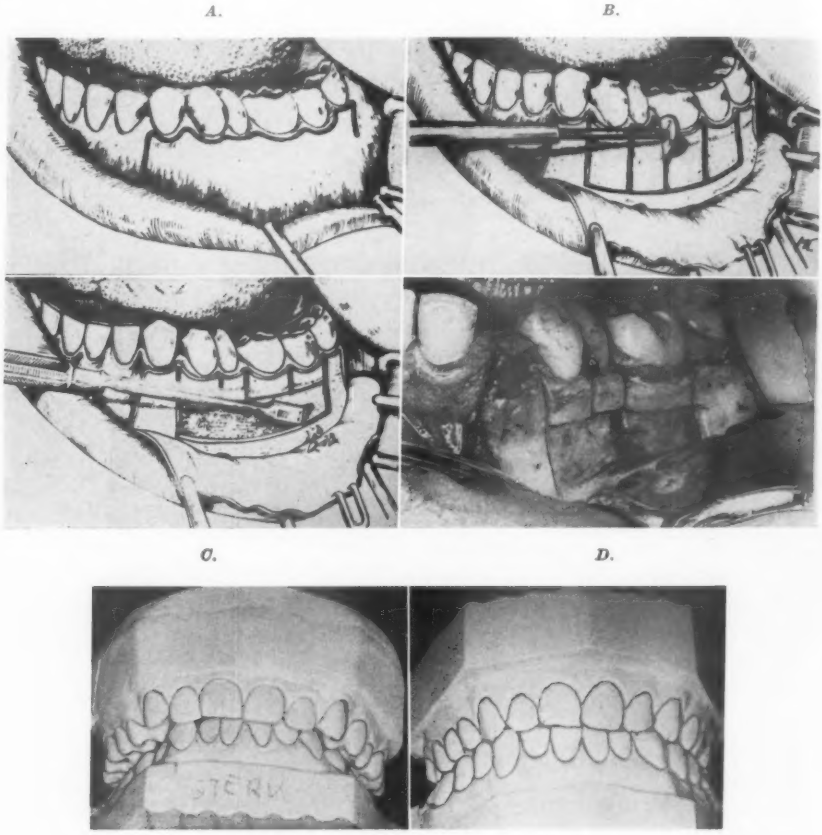
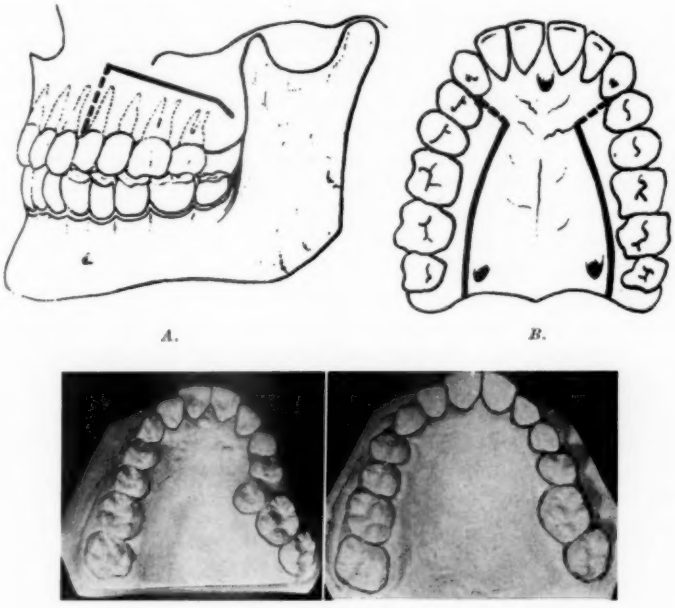


Fig. 41.—Sketch showing corticotomy for mandibular linguoversion. *A* to *D*, Photographs of operation. *E*, Plaster model before treatment. *F*, Plaster model after two months of treatment.

Contraction of the Maxilla.—A lateral extension of the maxilla by the same method as for the mandible is possible. The palatorrhapheal rupture is the only orthodontic method by which quick results may be achieved in

patients 16 years of age or younger. Therefore, I have used this supporting surgery only in one case. After an incision of the gingival margin, the bone is exposed. It is cut throughout, 1 cm. above the apices, with a sharp fine osteotome. The maxillary antrum is thus opened without any consequences. The corticotomy of the zygomatico-alveolar crest is extremely important, but it must not be carried completely around the posterior walls of the maxilla. The palatal bone is cut throughout into the maxillary antrum, laterally to the median sulcus. A corticotomy is performed interdentally on the alveolar process. Eight days later an appliance with cast-cap splints and an extension screw is cemented to the teeth. The result of the treatment is achieved in approximately eight weeks (Fig. 42).



A. *B.*

C. *D.*

Fig. 42.—Contraction of the maxilla. Sketch of the corticotomy (*A* and *B*) and models before (*C*) and after (*D*) treatment for three months.

Correction of Too Wide a Maxilla.—It is possible by the same means to narrow a maxilla that is too large. An adequate strip of bone is removed on the palate. The treatment is analogous to the extension of the maxilla, but the extension screw is inserted wide open and activated by screwing it tight.

CONCLUSION

It may be concluded that with all the surgical interventions at our disposal, with or without short subsequent orthodontic treatment, it is possible to correct every malposition of the teeth and every malformation of the jaws.

These surgical methods, which are not dangerous, should help adults and those who have had unsatisfactory results from orthodontic treatment. Today no patient should be released if orthodontic treatment turns out to be unsatisfactory. It should be the duty of the practitioner to point out to the patients that they may still benefit from a surgical operation.

SUMMARY

In spite of the great progress in orthodontics, there is still a large number of adult patients with malposition of teeth or jaws. Treatment is seldom possible without the help of surgical interventions in patients older than 16 years.

A survey of the orthodontic operations on the alveolar process is given. It is based on the results observed over several years on a large number of patients treated in our clinic. The procedures are divided into operations completely replacing orthodontic treatment and those facilitating it. The operation that protrudes the alveolar process in cases of alveolomandibular retrusion belongs to the first group. This method supplements the one recommended by Hofer with its mucosal incision which circumvents the mental nerve and includes circumferential wiring. The surgical correction of maxillary protrusion is explained; a means to eliminate the long postoperative orthodontic treatment for correction of the deep overbite is pointed out. The repositioning and the retention of the maxillary median fragment are accomplished according to the principles of treatment of jaw fractures.

I have presented my various methods for the correction of open bite. The last part of the article deals with my original method of surgery, which facilitates the orthodontic treatment for several dental malpositions. Corticotomy of maxillary and mandibular bone facilitates the displacement by subsequent orthodontic appliances either of a single tooth or of a group of teeth with their alveolar process. This saves precious time, and the danger of relapse is lessened.

REFERENCES

1. Ascher, F.: Zum Problem der chirurgischen Mobilisierung des prognathen Oberkiefer-Mittelstückes usw, Fortschritte der Kiefer- u. Gesichts-Chirurgie, Band I, Stuttgart, 1955, Georg Thieme Verlag.
2. Ascher, F.: Zur Spätbehandlung der Prognathie des Oberkiefers, Deutsche Ztschr. f. Zahnh. 7: 542, 1947.
3. Axhausen, G.: Beitrag Mund- und Kieferchirurgie, Leipzig, 1932, Johann Ambrosius Barth Verlag, Band IV, p. 742.
4. Bichlmayr, A.: Chirurgische Orthopädie, Z. zahnärztl. Orthopädie, 1930, H. 5.
5. Bichlmayr, A.: Chirurg. Kieferorthopädie und das Vorhalten des Knochens und der Wurzelspitzen nach derselben, Deutsche Zahn. Wchnschr., p. 835, 1931.
6. Bichlmayr, A.: Zur Spätbehandlung der Kieferanomalien, Deutsche Zahn. Wchnschr., p. 2, 1942.
7. Bichlmayr, A.: Über chirurg. Orthopädie bei Behandlung der Spätfälle, Deutsche Zahn. Wchnschr., p. 46, 1942.
8. Cohn-Stock: Chirurg. Immediatregulierung der Kiefer, Vrtljschr. Zahnh., 1921.
9. Converse, J. M., and Shapiro, H. H.: Bone Grafting in Malformations of the Jaws, Am. J. Surg. 88: 858, 1954.
10. Converse, J. M., and Shapiro, H. H.: Treatment of Developmental Malformations of the Jaws, Plast. & Reconstruct. Surg. 10: 473, 1952.

11. Eiselsberg, A., and Pichler, H.: Ersatz von Kiefer- und Kinnhautdefekten, Arch. klin. Chir. **2**: 122, 1912.
12. Hofer, O.: Die vertikale Osteotomie zur Verlängerung des einseitig verkürzten aufsteigenden Unterkieferastes, Ztschr. Stomatol. **34**: 826, 1936.
13. Hofer, O.: Operation der Prognathie und Mikrogenie, Deutsche Zahn-, Mund-, u. Kieferh. **9**: 121, 1942.
14. Holler, W.: Indikation und Technik der operativen Behandlung der Prognathie, Fortschritte der Kiefer- und Gesichts-Chirurgie, Band I, Stuttgart, 1955, Georg Thieme Verlag.
15. Immenkamp, A.: Die chirurg. orthopäd. Behandlung der Prognathie, Zahnärztl. Rundschau, **44**: 1438 and **46**: 1510, 1941.
16. Immenkamp, A.: Chirurg. Kieferorthopädie, Handbuch der Zahn- Mund- u. Kieferheilkd. vol. 3, Wien, 1958, Urban & Schwarzenberg.
17. Kazanjian, V. H.: Surgical Correction of Deformities of the Jaws and Its Relation to Orthodontia, Am. J. Orthodontics & Oral Surg. **22**: 259, 1936.
18. Kazanjian, V. H.: The Interrelation of Dentistry and Surgery in the Treatment of Deformities of the Face and Jaws, Am. J. Orthodontics & Oral Surg. **27**: 11, 1941.
19. Kazanjian, V. H.: Open-Bite Deformities of the Jaws—Surgical Treatment, Fortschritte der Kiefer- u. Gesichts-Chirurgie, Band II, Stuttgart, 1956, Georg Thieme Verlag.
20. Kazanjian, V. H., and Converse, J. M.: Surgical Treatment of Facial Injuries, Baltimore, 1949, Williams & Wilkins Company.
21. Korkhaus, G.: Handbuch der Zahnheilkunde, München, 1939, J. F. Bergmann.
22. Kostecka, F.: Progenie, Cechoslovenska Stomatol. **40**: 511, 1940.
23. Neumann, D.: Die Bichlmayr'sche Keilresektion bei der kieferorthopädischen Spätbehandlung, In Schuchardt, K., and Wassmund, M. (editors): Fortschritte der Kiefer- und Gesichts-Chirurgie, Band I, Stuttgart, 1955, Georg Thieme Verlag.
24. Obwegeser, H.: The Surgical Correction of Mandibular Prognathism and Retrognathia With Consideration of Genioplasty. Part I, ORAL SURG., ORAL MED. & ORAL PATH. **10**: 677-689, 1957.
25. Pichler, H., and Trauner, R.: Lehrbuch der Mund- und Kieferchirurgie, Wien, 1948, Urban & Schwarzenberg.
26. Skogsborg, C.: Die permanente Fixierung der Zähne nach orthodontischer Behandlung, Vrtlj. f. Zahnh. **4**: 278, 1926.
27. Schuchardt, K.: In Bier, Braun, and Kümmel: Chirurgische Operationslehre, Leipzig, 1954, Johann Ambrosius Barth, Band II. Operationen im Gesichts-Kieferbereich.
28. Schuchardt, K.: Chirurgische Orthopädie der Kiefer, Deutsche Zahn-, Mund-, und Kieferhkd. **9**: 73, 1942.
29. Schuchardt, K.: Die Chirurgie als Helferin in der Kieferorthopädie; Fortschritte der Kieferorthopädie, Stuttgart, 1954, Georg Thieme Verlag.
30. Schuchardt, K.: Formen des offenen Bisses und ihre operativen Behandlungsmöglichkeiten, Band V, Stuttgart, 1955, Georg Thieme Verlag.
31. Spanier: Prognathie-Operationen, Zahn. Orthopädie 1932.
32. Thoma, K. H.: Oral Surgery, St. Louis, 1958, The C. V. Mosby Company, Vol. II, p. 1388.
33. Trauner, R.: The Surgical Correction of Mandibular Prognathism and Retrognathia With Consideration of Genioplasty. Part II, ORAL SURG., ORAL MED. & ORAL PATH. **10**: 899-909, 1957.
34. Trauner, R.: Die retrocondyläre Implantation usw, Deutsche Zahn-, Mund-, u. Kieferh. **20**: 391, 1954.
35. Trauner, R.: Eine neue operative Methode beim Distalbib, Deutsche Zahn-, Mund-, u. Kieferh. **21**: 391, 1954; **22**: 475, 1955.
36. Trauner, R., and Obwegeser, H.: Zur Operationstechnik usw, Deutsche Zahn-, Mund-, u. Kieferh. **23**: 1, 1955.
37. Trauner, R., and Češnik, F.: Die Operationen beim Distalbib, und der Mikrogenie, Fortschr. Kiefer- und Gesichts-Chirurg. **1**: 211, 1955.
38. Wassmund, M.: Lehrbuch der praktischen Chirurgie des Mundes und der Kiefer, Band I, Leipzig, 1935, Johann Ambrosius Barth.
39. Stout: Cited in Thoma, K. H.: Oral Surgery, St. Louis, 1948, The C. V. Mosby Company, Vol. I, p. 526.
40. Dingmann, R. O.: Surgical Correction of Developmental Deformities of the Mandible, Plast. & Reconstruct. Surg. **3**: 124, 1948.
41. Blair, V. P.: Cited in Thoma, K. H.: Oral Surgery, St. Louis, 1948, The C. V. Mosby Company, Vol. II, p. 1456.

PREVENTION OF OSTEORADIONECROSIS OF THE JAWS

David S. Topazian, D.D.S., Philadelphia, Pa.*

THE phenomenon of osteoradionecrosis of the jaws has long been known as a serious complication of radiation therapy of malignant tumors of the oral cavity, pharynx, and face. Described by Regaud[21, 22] in 1922, this disease process has compromised the clinical results of radiation therapy in many cases and has, on occasion, caused the death of the patient.[2, 8, 20]

The fact that osteoradionecrosis occurs even with modern therapeutic advances in the control of infection implies that a review of its causes and some suggestions for its prevention would be in order.

Radiation in therapeutic doses destroys or impairs the vitality of bone. The bone thus affected loses its normal defensive barriers to infection and its normal reparative properties after infection or trauma. Anyone concerned with the treatment of diseases of the oral cavity should be aware of the effects of irradiation on oral tissues and should appreciate the fact that irradiated tissues must be approached with care and caution. Thus, he can help to prevent the patient who has been free of obvious cancer for a number of years from being subjected to pain, disfigurement, and even death which may result from osteoradionecrosis of the jaws.

EFFECTS OF IRRADIATION ON TISSUES

The basic reaction of cells exposed to x-rays is that of ionization. This varies with the amount of irradiation, the speed of absorption, and the relative radiosensitivity of the tissue. Water is broken down into hydrogen and oxygen ions, oxidative processes cease, and enzymes are inactivated. Coagulation of chromatin and disintegration of the cell nucleus result in damage to the genetic apparatus and subsequent vacuolization and necrosis.

The difference in sensitivity of various tissues to irradiation is apparent. Young cells are more sensitive than mature cells and endothelial or epithelial cells are more easily affected than connective tissue cells. Cartilage is more sensitive than bone, whereas muscle and nerve are the most resistant tissues.[15]

Soft Tissues.—Therapeutic doses of irradiation often cause inflammation of skin and mucous membranes. Edema, dilation of vessels, and a reduction in intercellular substance result in erythema and epilation of skin clinically.

*Resident in Oral Surgery, Philadelphia General Hospital.

Massive doses of x-ray may produce swelling, edema, exudation, ulceration, and necrosis.[15] In the oral cavity an epithelitis is observed, and gingival recession may occur.[26]

Bone.—Ewing[10] stated that practical effects of irradiation are due largely to the production of vascular disturbances which result in decreased blood supply to the tumor. Bone is similarly involved by a decrease in its circulation.

Vacuolization and swelling of the endothelial cells and of all cells of the blood vessel wall lead to occlusion of the vessel. The bone marrow thus deprived of blood becomes "an ill nourished mass of mucinous fat and fibrous tissue." Ewing observed that the periosteum was thickened and stripped easily away from bone and that there was a notable lack of osteoblasts along the inner surface of the periosteum.

McCrorie[17] theorized that the lethal dose of irradiation was less for osteoblasts than for osteoclasts allowing unopposed osteolysis.

Watson and Scarborough[31] suggested that the high calcium content of bone is partly responsible for transforming the hard, penetrating primary radiation to a less penetrating, more absorbent, more caustic type of secondary radiation. The osteoblasts of the periosteum receive both primary radiation and the maximum effect of the caustic secondary rays.

MacLennan[14] noted that endarteritis and periarteritis are constant findings in all established cases of osteoradionecrosis with fibrous thickening of all vessel coats, disruption of elastic fibers, and predisposition to thrombus formation.

Bone thus reduced in vitality by irradiation not only loses its ability to repair and regenerate because of a lack of osteoblasts but it also presents very favorable conditions for the growth of bacteria throughout the Haversian systems and canaliculi.[9] It may retain its normal macroscopic and radiographic appearance.[2, 13] It is actually nonvital, but necrosis does not usually occur unless there is superadded infection.[30] Infection leads to slow degeneration and formation of a sequestrum without any reparative reaction.[8]

Teeth.—According to del Regato,[20] patients whose teeth have remained in perfect condition over a long period of time following irradiation to the mouth, pharynx, and larynx are exceptional. Del Regato noted that following the initial treatments patients develop sensitivity to heat, cold, and sweets, a feeling of elongation of teeth, and a diminution in salivary secretion. These symptoms disappear, only to reappear in six to eight months.

In a small group of patients the initial picture was progressive and associated with carieslike lesions at the cementoenamel junction, culminating in rapid destruction of all teeth twelve to eighteen months after treatment. More frequently, however, there appeared in four to eight years superficial caries, beginning at the necks of the teeth on the labial and buccal surfaces and progressing to fracture of the unaffected crown.

Del Regato also noted very rapid occlusal and incisal wearing of the teeth. These carieslike and attritive lesions occurred even when the teeth were entirely outside the field of irradiation. There was usually some degree of diminution of salivary secretion as well as a notable rise in the salivary acidity.

Sharp,[25] on the other hand, noted little change in pH after irradiation. Because of the soft tissue slough which acted as a medium for the habitat of acidogenic bacteria and yeasts, the most significant acidic change occurred immediately following irradiation.

Stafne and Bowing[27] observed that a large number of patients who had received irradiation affecting the salivary glands had acquired the habit of holding fruit drops or other acidic confections in their mouths almost continually to relieve a sensation of dryness or a metallic or other taste. They thought that the resultant carious lesions were like those observed in patients with similar habits who had received no irradiation.

It can be readily appreciated that teeth affected with this peculiar type of destruction are almost certain to cause some type of postirradiation difficulty in the form of pain, fracture, or infection.

PATHOGENESIS OF OSTEORADIONECROSIS

Osteoradionecrosis occurs more frequently in the mandible than in the maxilla.[2, 8] MacLennan[14] has stated that 83 per cent of the cases affect the mandible, chiefly because the greater number of irradiated lesions occur in proximity to the mandible and because its main blood supply is composed of one large vessel. On the other hand, the maxilla has a wealth of anastomoses which would tend to nourish any bone whose blood supply was diminished.

Although cases of osteoradionecrosis occurring spontaneously after irradiation have been reported,[13] certain other predisposing factors are generally thought necessary.[11] La Dow[12] has defined the general factors as (1) intensive x-ray or radium therapy, (2) trauma to the structures in the treated areas, and (3) infection from the oral flora.

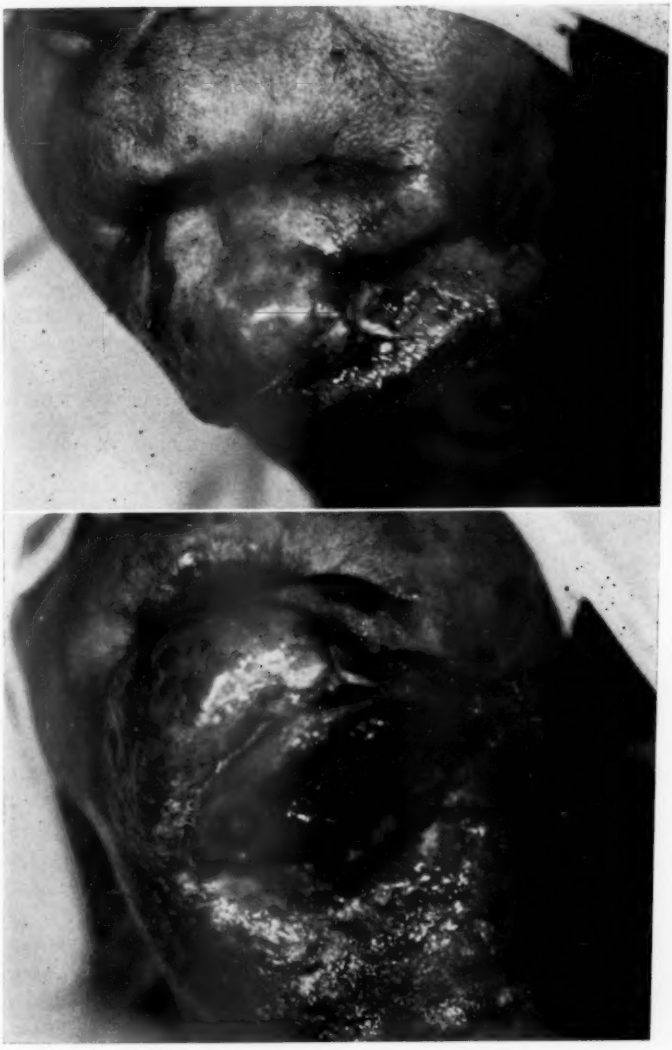
Because of the pain and sensitivity of any teeth in the treated area, the source of trauma in a jaw that has been subjected to intense irradiation is most often the extraction of a tooth. However, other sources of trauma are of great importance. These include irritation and ulceration by a denture, toothpick trauma, and chewing of rough foods.[2, 29] These factors may cause a soft tissue wound that will allow bacterial invasion of the deeper structures.

The source of infection may often be teeth which have been subjected to irradiation and which have undergone carious change and coronal fracture with pulpal involvement.

Poor oral hygiene commonly found after radiotherapy, inanition, the tendency toward loss of resistance to infection by the patient, and the altered properties of bone result in the clinical picture of osteoradionecrosis which Ellinger[8] has described as "a fulminant, painful and sequestrizing osteomyelitis which shows a long, drawn out course in view of the absence of periosteal bone formation."

The acute symptoms include deep boring pain, trismus, swelling, and eventually the development of soft tissue abscesses and draining sinuses.[29] Ulceration of the skin or oral mucosa may cause exposure of large portions of necrotic bone. In severe cases the sequestrum formed may consist of the entire mandible[2] (Fig. 1).

A.



B.

Fig. 1.—*A*, A case of osteoradionecrosis of the mandible which followed irradiation for cancer and subsequent tooth extraction without antibiotic prophylaxis. The sequestrum consisted of almost the entire mandible.

B, The same case as above, showing exposure of the tongue and floor of the mouth through the soft-tissue slough. (Courtesy of Dental Department, Philadelphia General Hospital.)

PREVENTION OF OSTEORADIONECROSIS

In the light of the etiology and pathogenesis of this complication of cancer therapy, prophylactic measures may be considered at the various levels of treatment—that is, before radiotherapy is initiated, during radiotherapy, and for the entire survival period after the radiotherapy has been completed.

Preirradiation Prophylaxis.—The extraction of all teeth which will be potential sources of infection is probably one of the greatest single steps in the prevention of osteoradionecrosis. Most authors agree that all carious and infected teeth as well as all teeth, carious or not, in the direct line of the rays or on the side of the lesion to be treated should be extracted.[2, 5-8, 11, 12, 14, 20, 23, 24, 28, 29, 31] Others recommend extraction of all teeth,[11, 13] especially if the salivary glands are to be irradiated or if the patient shows general neglect.[26]

Castigliano[2] states that the number of teeth to be removed depends on the manner in which the radiation is to be delivered. If large portals of treatment are to be used, all teeth should be extracted. If the insult to the jaw is small or if the alveolar structure can be afforded complete protection with an intraoral cone, only the teeth directly affected or those which will interfere with the introduction of such a cone should be removed.

It is probably better to remove too many teeth than too few. Castigliano notes that "a handful of teeth is not worth a life." He further states that the extraction of teeth need not be given such serious consideration when the patient is in the terminal stages of disease and his survival is measured in terms of a few months.

After the extractions have been performed, the field should be thoroughly débrided to minimize the chances of postoperative ulceration by spicules of bone or debris, and the soft tissues should be approximated in an effort to promote early healing, so that radiotherapy might be begun ten to fourteen days after this procedure.[2, 8, 13]

During the healing period measures should be taken to ensure adequate oral hygiene. Thorough scaling of all remaining teeth has been recommended.[11, 26]

The question has arisen as to whether the delay of ten to fourteen days before beginning irradiation of a malignant neoplasm is justified. A few authors feel that valuable treatment time will be lost and that extraction of teeth may cause further dissemination of the tumor.[19, 32]

Sarnat and Schour[23] feel that the loss of time in waiting for healing will be compensated for by reducing the chances of secondary infection and by making the treatment generally safer. Ellinger[8] states that the delay is entirely justified because of the seriousness of the jaw necrosis. In 235 cases of osteoradionecrosis reported by Watson and Searborough,[31] twelve patients who were free of cancer died as a direct result of jaw necrosis.

Prophylaxis During Radiotherapy.—The irradiation of malignant lesions is mainly the concern of the radiotherapist, but the oral surgeon should be aware of certain measures which are of value in protecting the teeth and jaws during treatment of head and neck lesions. The likelihood and the severity of osteoradionecrosis vary directly with the size of the treatment portal used. The

greater the amount of the mandible irradiated, the more likely is the development of necrosis and the more severe it will be.[2] The portals of treatment, therefore, should be as small as will adequately cover the lesion and be consistent with rational therapy.[2, 6, 16]

Use of sublabial lead shields in the radiotherapy of lip and cheek lesions will protect the teeth and jaws. A technique has been described for the construction of facial casts upon which lead masks are swaged. These are used in the treatment of carcinoma of the skin of the face.[3] Precision individualized lead cones for peroral irradiation which confine the exposure to the lesion and protect the alveolar structure have also been devised.[4] The use of these various devices has significantly reduced the incidence of jaw necrosis.[2]

At this stage of treatment the radiotherapist and the attending oral surgeon should advise the patient of the grave consequences of any surgical procedure or trauma to his irradiated jaw. This may help to preclude any surgical procedure before due precautions have been taken.

Postirradiation Prophylaxis.—Since the majority of the cases of osteoradionecrosis reported in the literature have been associated with the extraction of teeth or other trauma following x-ray or radium therapy, it behooves the dentist to treat painful teeth and traumatic lesions with considerable conservatism. The bone of the jaws may appear to be normal radiographically and clinically, making it impossible to evaluate its relative viability.

Seldin, Rakower, and Selman[24] have advised that in order to delay extractions, nerve block with long-acting anesthetics or alcohol be used in the treatment of postirradiation pain. Extirpation of the pulp and root canal filling have also been recommended.[26, 31]

The length of time that extractions should be delayed after radiotherapy varies widely. Cutler[6] advises a delay of several years. Kanthak[11] states that extractions should be performed only after an indeterminate period of time. Castigliano[2] feels that at no time is the extraction of teeth to be considered a safe procedure.

Cook[5] has reported a case in which osteoradionecrosis of the mandible due to denture irritation occurred thirteen years after the patient's last exposure to radium. On the other hand, Wildermuth and Cantril[32] have reported cases of postirradiation extractions six months after treatment with no apparent ill effects.

Inasmuch as denture irritation may precipitate necrosis, Thoma[29] states that patients who have been irradiated should get along without dentures if at all possible. Castigliano[2] recommends that wearing of dentures be delayed for at least eighteen to twenty-four months after treatment involving the alveolar ridges, buccal surfaces, or lateral borders of the tongue.

After treatment, oral hygiene and the general health of the patient must be carefully sustained in order to prevent infection. The epithelitis and pain produced by radiotherapy often cause a loss of appetite and an indifferent attitude toward oral health.

La Dow[12] and MacLennan[14] advise the use of frequent bland mouthwashes, such as 1.5 per cent sodium bicarbonate, to remove debris. The general physical

condition of the patient may be improved by a 3,500 to 4,000 calorie diet with high fat content to minimize volume. This may be given in frequent feedings or by tube if indicated.

When extractions cannot be delayed further, they should be performed with a minimum of trauma and with full antibiotic coverage after the patient has received supportive treatment to ensure optimum physical condition.

The use of elastics to remove teeth with a minimum of trauma has been advocated.[23, 26] The successful use of this technique and the method employed have been well described by Niebel and associates.[18]

THE IMPORTANCE OF THE HISTORY IN PROPHYLAXIS

The present-day public awareness of cancer, the alertness of dentists in recognizing early malignant lesions of the oral cavity, and the advances in radiotherapy have increased the number of treated patients who are clinically free of malignant disease a number of years after the original detection of a lesion. The literature contains a striking number of case reports of such patients who have had teeth extracted without proper precautions and who have subsequently become victims of osteoradionecrosis of the jaw. Therefore, it is suggested that a part of the routine history taken before every oral surgery procedure be devoted to a few questions concerning radiotherapy.

Cook[5] has reported a case in which the patient told his dentist that he had had cancer but had been cured. In this case an extraction without necessary precautions precipitated eventual necrosis of the jaw.

Cutler[6] states that cases of osteoradionecrosis have occurred in women after x-ray therapy for the removal of superfluous facial hair and subsequent dental treatment. He feels that multiple extractions or even periodontal treatments in such a case without proper preoperative and postoperative care might eventually cause the death of the patient.

Patients may not consider radium treatments when questioned about radiotherapy. Therefore, it is suggested that the patient be thoroughly interrogated concerning both x-ray and radium treatments. Furthermore, any history of malignant disease about the head and neck should evoke an attempt to seek consultation and defer any surgical intervention.

In cases in which there is a history of x-ray or radium therapy it is imperative that the radiotherapist who administered treatment be consulted.[2] The period that has elapsed since treatment, the amount of irradiation delivered, the size of the portals of treatment, and the areas irradiated affect the prognosis following tooth extraction.

SUMMARY AND CONCLUSIONS

A review of the literature on the effects of irradiation on soft tissues, bones, and teeth and the pathogenesis of osteoradionecrosis has been presented. The following factors should be considered in an understanding of the prevention of osteoradionecrosis at various levels of radiotherapy:

Preirradiation:

1. All carious and infected teeth and all teeth, infected or not, in the direct line of the rays or on the side to be treated should be extracted.

2. All teeth should be extracted if the salivary glands are to be irradiated for cancer, if the patient exhibits oral neglect, or if wide portals of treatment are to be used.

3. Following extractions, the wounds should be carefully débrided and the soft tissues approximated.

4. A delay of ten to fourteen days before beginning radiotherapy is justified to allow healing to begin.

During Irradiation:

1. The smallest possible portals of treatment consistent with rational therapy should be used to minimize the amount of the jaw irradiated. This will reduce the likelihood of development of osteoradionecrosis and its severity, should it occur.

2. Intraoral cones, lead face masks, and sublabial shields should be used when possible during treatment in order to confine the irradiation to the lesion and protect alveolar structures.

3. The patient being treated with x-rays or radium should be warned of the consequences of surgical intervention without proper precautions and of the consequences of trauma to his irradiated jaw.

Postirradiation:

1. Painful teeth must be treated conservatively, even though the bone appears to be normal radiographically and clinically.

2. Nerve block with long-acting anesthetics or alcohol may be used to control pain and delay extractions.

3. Teeth in the irradiated field with fractured crowns may be treated with root canal fillings in order to postpone extractions.

4. The extraction of teeth from an irradiated jaw is never to be considered an entirely safe procedure.

5. In addition to tooth extraction, other forms of trauma, such as denture irritation or gingival laceration by toothpicks or rough food, may initiate jaw necrosis. Dentures should not be worn on an irradiated jaw for at least eighteen to twenty-four months.

6. Oral hygiene and the general health of the patient must be maintained following therapy to minimize the possibility of infection. The patient should be advised of the necessity of frequent dental examinations.

7. If tooth extraction is imperative, the patient should first receive supportive therapy and full antibiotic coverage. The use of elastics is an excellent technique for atraumatic removal of teeth.

8. Surgery should not be performed without consultation with the radiotherapist who treated the patient originally.

9. It is suggested that questions concerning x-ray and radium treatments be included in the routine history taken before any oral surgery procedure.

REFERENCES

1. Burket, L. W.: Oral Medicine, Philadelphia, 1957, J. B. Lippincott Company.
2. Castigliano, S. G.: In Burket, L. W.: Oral Cancer, Philadelphia, 1957, J. B. Lippincott Company, p. 455.
3. Castigliano, S. G., and Gross, P. P.: Master Metal Facial Cast for Swaging Lead Masks in the Treatment of Carcinoma of the Skin of the Face, Am. J. Orthodontics & Oral Surg. **33**: 319, 1947.
4. Castigliano, S. G., and Sklaroff, D. M.: Use of Precision Cones in Peroral Irradiation, Am. J. Roentgenol. **54**: 968, 1950.
5. Cook, T. J.: Late Radiation Necrosis of the Jaw Bones, J. Oral Surg. **10**: 118, 1952.
6. Cutler, M.: The Problem of Extractions in Relation to Osteoradionecrosis Complicating Radiotherapy for Intraoral Cancer, ORAL SURG., ORAL MED. & ORAL PATH. **4**: 1077, 1951.
7. Daland, E. M.: The Surgical Treatment of Postirradiation Necrosis, Am. J. Roentgenol. **46**: 287, 1941.
8. Ellinger, F.: Medical Radiation Biology, Springfield, Ill., 1957, Charles C Thomas.
9. Ewing, J.: Radiation Osteitis, Acta radiol. **6**: 399, 1926.
10. Ewing, J.: Tissue Reactions to Radiation, Am. J. Roentgenol. **15**: 93, 1926.
11. Kanthak, F. F.: X-ray Irradiation and Osteonecrosis of the Jaws, J. Am. Dent. A. 28: 1925, 1941.
12. La Dow, C. S.: Osteoradionecrosis of the Jaw, ORAL SURG., ORAL MED. & ORAL PATH. 3: 582, 1950.
13. Lawrence, E. A.: Osteoradionecrosis of the Mandible, Am. J. Roentgenol. **55**: 733, 1946.
14. MacLennan, D. W.: Some Aspects of the Problem of Radionecrosis of the Jaws, Proc. Roy. Soc. Med. **48**: 1017, 1955.
15. Macomber, W. B., Wang, M. K. H., Trabue, J. C., and Kanzler, R.: Irradiation Injuries, Acute and Chronic and Sequelae, Plast. & Reconstruct. Surg. **19**: 9, 1957.
16. Martin, H. E., and Sugarbaker, E. L.: Cancer of the Floor of the Mouth, Surg. Gynec. & Obst. **71**: 347, 1940.
17. McCrorie, W. D. C.: Fractures of the Femoral Neck Following Pelvic Irradiation, Brit. J. Radiol. **23**: 587, 1950.
18. Niebel, H. H., Neenan, E. W., Walsh. R. P., and Weimer, J. B.: Removal of Teeth From Irradiated Tissue, J. Oral Surg. **15**: 313, 1957.
19. Paterson, R.: The Treatment of Malignant Disease by Radium and X-rays, Baltimore, 1948, Williams & Wilkins Company.
20. Del Regato, J. A.: Dental Lesions Observed After Roentgen Therapy in Cancer of the Buccal Cavity, Pharynx and Larynx, Am. J. Roentgenol. **42**: 404, 1939.
21. Regaud, C.: Sur la nécrose des os atteints par un processus cancéreux et traités par les radiations, Compt. rend. Soc. biol. **87**: 427, 1922.
22. Regaud, C.: Sur la sensibilité du tissue osseux normal vis á vis des rayons X et gamma et sur le mécanisme de l'osteoradionécrose. Compt. rend. Soc. biol. **87**: 629, 1922.
23. Sarnat, B. G., and Schour, I.: Oral and Facial Cancer, Chicago, 1957, Year Book Publishers, Inc.
24. Seldin, H. M., Rakower, W., and Selman, A. J.: Radio-osteomyelitis of the Jaw, J. Oral Surg. **13**: 112, 1955.
25. Sharp, G. S.: The pH of Human Mixed Saliva During Irradiation of Intraoral Carcinoma, Am. J. Roentgenol. **25**: 266, 1931.
26. Sleeper, E. L.: Prophylactic Dental Treatment Prior to Irradiation of the Jaws, Alpha Omegan **44**: 101, 1950.
27. Stafne, E. C., and Bowing, H. H.: The Teeth and Their Supporting Structures in Patients Treated by Irradiation, Am. J. Orthodontics & Oral Surg. **33**: 567, 1947.
28. Stewart, M. B.: Osteoradionecrosis and Cancer of the Head and Neck, Arch. Otolaryng. **38**: 407, 1943.
29. Thoma, K. H.: Oral Surgery, St. Louis, 1952, The C. V. Mosby Company.
30. Warren, S.: Effects of Radiation on Normal Tissues. XII. Effects on Bone, Cartilage, and Teeth, A. M. A. Arch. Path. **35**: 323, 1943.
31. Watson, W. L., and Scarborough, J. E.: Osteoradionecrosis in Intraoral Cancer, Am. J. Roentgenol. **40**: 524, 1938.
32. Wildermuth, O., and Cantril, S. T.: Radiation Necrosis of the Mandible, Radiology 61: 771, 1953.

DERMOID CYST OF FLOOR OF MOUTH

Report of a Case

Marcos Dones, D.D.S., B.S., San Juan, Puerto Rico*

DERMOID cysts are of congenital origin and are closely related to teratomas, tumors containing all the primary histologic types of tissue. Accordingly, all dermoid cysts contain some of the following structures or tissues: hair and hair follicles, teeth, nails, sweat glands, brain tissue, and many other structures. Dermoid cysts occur principally in the testes and ovaries, although they may be found at any fusion point of the human body. Shore[1] reported only two dermoid cysts arising in the floor of the mouth of 54,000 surgical specimens examined. Meyer[2] has reported four such cases. It is very rare, therefore, to find a dermoid cyst arising in this location. The signs presented by this type of cyst are painless swelling in the floor of the mouth, upward displacement of the tongue, sensation of fullness in the mouth, and sometimes dyspnea.

CASE REPORT

The patient, a healthy 22-year-old man with some difficulty in speech and swelling in the floor of the mouth (Fig. 1), was admitted to Mimiya Hospital on March 14, 1957, for excision of a tumor in the floor of the mouth. The physical and laboratory examinations were essentially negative, and the past history was noncontributory.

On the day following admission, the patient was taken to the operating room where, under local anesthesia, a transverse incision was made in the floor of the mouth and the mucous membrane was mobilized to expose the cyst membrane. The thick membrane of the cyst was grasped with Allis forceps, and the excision was carried out by sharp and blunt dissection (Fig. 2). The sac contained some fluid and a considerable amount of cheesy material and hair. The deep tissues were closed with catgut, and the mucous membrane of the floor of the mouth was sutured with interrupted 000 black silk (Fig. 3). The recovery was uneventful.

Pathologic Examination.—

Gross: The cyst measured 3.5 cm. in diameter. The inner lining was somewhat granular, but the contents of the cyst had been previously evacuated. Several sections were taken through different levels.

*Oral Surgeon Attending, San Juan City Hospital, Department of Surgery, University of Puerto Rico School of Medicine.

Fig. 1.

Fig. 2.

Fig. 3.

Microscopic: The cyst showed stratified squamous epithelial lining producing abundant keratin beneath this lining; in areas there were numerous sebaceous glands and occasional hair follicles (Fig. 4).

Diagnosis: Dermoid cyst of floor of mouth.

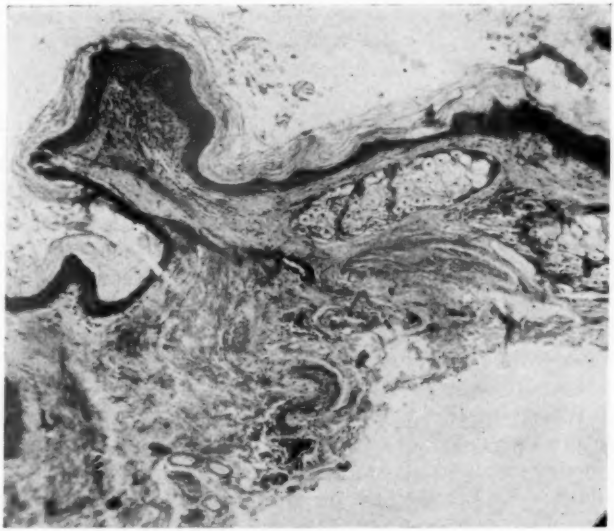


Fig. 4.

CONCLUSION

Complete excision is the treatment of choice for dermoid cyst.

REFERENCES

1. Shore, B. R.: Sublingual Epidermoid Cysts, Ann. Surg. 108: 305, 1938.
2. Meyer, I.: Dermoid Cysts (Dermoids) of the Floor of the Mouth, ORAL SURG., ORAL MED. & ORAL PATH. 8: 1149, 1955.

EXODONTIA

. . . . . .

CARE OF THE HEMOPHILIAC PATIENT IN DENTAL SURGERY

Aaron Finkelman, D.D.S., Philadelphia, Pa.*

THERE have been a number of articles in the newspapers in recent years about hemorrhage following tooth extraction, but there have been too few articles on this subject in the dental journals.

In many cases the hemophiliac (or his family) is not aware of his blood problem until a tooth, either deciduous or permanent, is extracted in a private office with subsequent massive bleeding. Physicians, dentists, and oral surgeons all have some pet method for the control of bleeding, but in serious cases of hemophilia these methods have not proved adequate.

At Jefferson Hospital we have a blood department which handles a large number of hemophiliacs who are under constant supervision and study. The dental staff performs the necessary dental surgery in cooperation with this department. In many cases removal of a tooth is the only reason for hospitalization.

Through the past years we have tried every material and technique which has come to our attention for tooth extraction and for postoperative treatment in these cases. In the course of handling some hundreds of extractions (including, for example, one case in which twenty-eight teeth were removed electively, requiring a four-year period to accomplish this work with several hundred transfusions of blood plasma, autogenous globulin, etc.), we have developed a technique which is simple but effective in almost all extractions in this type of patient.

PREOPERATIVE CONSIDERATIONS

A number of factors must be considered. First, the patient's history, medical and dental, has to be brought up to date. His blood picture is studied by a competent hematologist. A thorough dental prophylaxis is performed, occlusal adjustments are made to reduce trauma, and broken segments of roots or teeth are rounded off. Full-mouth x-ray pictures are an essential preliminary item.

*Head of Department of Oral Surgery, Jefferson Hospital.

An understanding of the reactions of the hemophiliac's oral tissues is important. The alveolar tissues about the socket of an extracted tooth in a true "bleeder" lack elasticity, that is, they do not close up as they would in a normal healthy person after extraction. Bleeding is not necessarily of a direct arterial type; there may be an oozing from the gingivae, which can be disturbing as to quantity and continuity of flow. The one favorable factor is a higher resistance to postoperative infection than in normal persons.

TECHNIQUE OF REMOVAL

The tooth area is infiltrated with a local anesthetic in close proximity to the tooth. We use a *very fine, short needle* that does not enter too deeply into the tissue; thus, needle trauma is reduced to a minimum. Block anesthesias may produce hematomas in the mandibular and tuberosity areas and in some cases have produced near-fatal results without any extractions having been done. In one mandibular block for operative dentistry a hematoma resulted, and a tracheotomy and twenty-four blood transfusions, plus other fluid adjuncts, were necessary before the patient recovered. Anesthesia has been limited to straight Novocain and Xylocaine with 1:100,000 epinephrine.

The gingival tissue should be separated from the tooth or root sufficiently to prevent tearing of the tissues during removal of the tooth. The actual removal of the tooth or root should be accomplished with the least possible trauma.

Due to the higher resistance to postoperative infection and the traumatic danger of curettage, we do not curette after extraction in hemophiliacs. At this point, mention should be made of coagulation by ionization, a treatment which we used with some success but which also produced some nasty failures. Gelfoam and other absorbable packs ball up and pop out of the socket in these cases. The one method which has given us the greatest success has been the use of iodoform gauze packed firmly like a gold-foil filling from one side of the socket to the other up to the surface of the gingivae. Overpacking and underpacking should be avoided in order that surface treatment may be administered in the event of seepage. Before placing the pack, we do not use any sterilization agent, such as Camphophenique or bone wax, as this would prevent adhesion of the pack to the bony socket.

Bleeding after extraction is generally not an immediate problem; in the worst cases secondary hemorrhage occurs, usually several days later, due to the lack of contraction of the tissue. In fact, in some cases there seems to be an expansion of the tissues about the extracted area. In one case the socket was overpacked, and bleeding occurred interstitially; this caused a hematoma below the border of the mandible which had to be relieved by total removal of the pack.

Surface bleeding has been controlled very satisfactorily by the use of light, wet, pressure packs of gauze with powdered bovine plasma placed against the bleeding area for long periods of time.

In a number of cases thrombin on pads of Gelfoam has helped control surface bleeding. The patient is kept in an almost sitting position in bed to prevent increased blood pressure in the head. In the more severe cases only intravenous feeding is undertaken for several days. In less severe "bleeders" liquid diet is prescribed until the risk of bleeding is at a minimum. Mouthwash and gauze are used for cleaning purposes.

In some cases a clot with a heavy membrane develops over the socket with the pack. This has a distinct use if the bleeding goes into the clot or if the clot is not broken, even if it becomes so large that the patient has to keep his mouth open rather wide at all times. The pressure which this clot creates acts backward on the socket area to which it is attached; if it remains whole for some six to nine days (in a very cooperative patient), it will begin to shrink and fall off like a dried prune, and the postoperative problem will have solved itself.

When the bleeding has been controlled by the internal pack (which has given us the best results so far) and the pack attempts to exfoliate after several days, it is not removed but is gradually cut down; sometimes as much as three weeks elapse before it is completely removed.

Because hemophiliacs differ from one another in their clotting and healing factors and vary individually at different times, it is up to the hematologist to decide the most propitious time for extraction. The amount of blood prepared in advance should be overestimated at all times. In one patient a minimum of three to five transfusions were required for several extractions. Yet, intermingled with these more or less simple extractions were some that required forty to fifty transfusions. The particular type of extraction was not a factor, but the same patient's response could not be gauged preoperatively. Incidentally, at no time have we considered more than one extraction at any one time; when possible, we generally have extracted a single-rooted tooth as the first of a series in order to determine the patient's reaction to dental surgery.

The following case report, with its medical aspects, should give sufficient warning to anyone foolhardy enough to extract a hemophiliac's teeth in the office or to consider multiple extractions for such a patient.

CASE REPORT

A 26-year-old white man needed to have twenty-eight teeth and roots extracted in order to pass a pre-employment physical examination as well as to eliminate dental infection seen clinically and in roentgenograms. After completion of all preliminary blood work, including preparation of a blood supply for transfusions, and after prophylaxis, it was decided that the necessary extractions should be undertaken in the face of a Class 4 "bleeder," the greatest surgical risk in the hemophilia category.

Preoperative medication consisted of vitamin K, 4.8 mg. per day; vitamin B complex, capsules twice daily; and ascorbic acid, 200 mg. three times a day. Fresh blood, 250 c.c. was given immediately before and immediately after the operation.

The totals (recorded in the history which, due to the problems involved, may be incomplete) for the twenty-eight extractions were as follows:

Whole blood—164 transfusions; volume, 70,100 c.c.
Plasma—8 transfusions; volume, 2,700 c.c.
Autogenous globulin—15 transfusions; volume, 6,950 c.c.
Saline and glucose—volume, 17,000 c.c. recorded (though probably much higher).

During eleven hospitalizations, ranging from three weeks to three months, one to four teeth were removed. Constant attention was given the blood picture during the periods between individual extraction and between returns to the hospital for further surgery.

It took three years and eight months to complete this work.

ORAL MEDICINE

. . . . . .

DENTAL OBSERVATIONS IN GAUCHER'S DISEASE

A Twenty-Year Follow-up

I. B. Bender, D.D.S., Philadelphia, Pa.*

THERE are many systemic diseases that exhibit bone changes upon x-ray examination. These changes manifest themselves throughout the skeletal system, and bone lesions can appear in the mandible or the maxilla just as readily as elsewhere in the body. The intraoral x-ray can therefore detect the presence of systemic diseases in many instances. Most of these diseases are chronic in nature. The patient quite often is not aware of any symptoms, and a routine dental x-ray examination often leads to detection of an organic disorder.

Some of these diseases manifest changes in the bone cortex, some in the cancellous portion, some in the long bones, and others in flat bone. There are various types of bone lesions. Some are expansile, producing an expansion of the cancellous structure with a thinning of the bone cortex as manifested in polyostotic fibrous dysplasia. In some there is an expansion of the bone cortex, as in infantile cortical hyperostosis. Some produce radiolucent lesions, as in hyperparathyroidism, while others produce radiopaque lesions, as in osteopetrosis. Some, as Paget's disease, manifest osteoporosis and osteosclerosis. Dental x-rays can serve to establish a definite or a tentative diagnosis, for some of these diseases have a particular predilection for certain parts of the skeleton.

Many of these diseases produce osseous changes that are expressions of derangement in the hematopoietic system, such as those observed in leukemia, Cooley's anemia, and sickle-cell anemia. Some express derangement as a result of systemic infection (for example, lues and tuberculosis). Anatomic defects, such as coaretation of the aorta and aneurysm, also will manifest changes with definite lesions in the mandible. Disturbances in vitamin, calcium, phosphorus, protein, and lipoid metabolism also produce changes in the

*Senior Attending Dentist, Albert Einstein Medical Center.

skeletal system, including the mandible and the maxilla. One of the diseases that exhibit osseous changes as an expression of derangement of lipoid metabolism is Gaucher's disease.

This is one of a group of diseases classified under the general heading of lipoid dystrophy. It is a disease of lipoid metabolism in which a generalized hyperplasia of lipoid cells takes place in the liver, spleen, lymph nodes, and bone marrow. Belonging to this group are Gaucher's, Schüller-Christian, Niemann-Pick, and Tay-Sachs diseases. Epstein and Lorenz[1] have shown that a particular lipoid metabolism is at fault in each of the foregoing diseases. Lieb[2] identified the lipoid at fault in Gaucher's disease, one of the cerebrosides, and called it kerasin. The lipoid substance kerasin is stored in the foam cells of the reticuloendothelial system, especially in the spleen and liver. These foam cells usually measure from 20 to 100 microns in diameter and are known as Gaucher's cells. These foam cells invade the spleen, liver, lymph nodes, bone marrow, and cortex.

The disease is usually predominant in the Jewish race, and it appears to be more frequent in the female sex in a ratio of 2:1. Clinically, it is characterized by a slow, chronic course, with a gradual increase in the size of the spleen which in some instances reaches enormous proportions (Fig. 1). This is followed by an enlargement of the liver. The superficial lymph nodes remain normal in size. The continued enlargement of the spleen quite often necessitates a splenectomy at some future date.

Fig. 1.—Note the splenic enlargement. Splenectomies are usually performed for mechanical reasons, as above, or to prevent hemorrhagic complications.

The patient develops certain blood changes. First, there is a leukopenia, followed by hypochromic or macrocytic anemia. There is a thrombocytopenia which is related to the hemorrhagic diathesis characterizing the late stages of the disease. Bleeding and coagulation times are usually normal, provided that

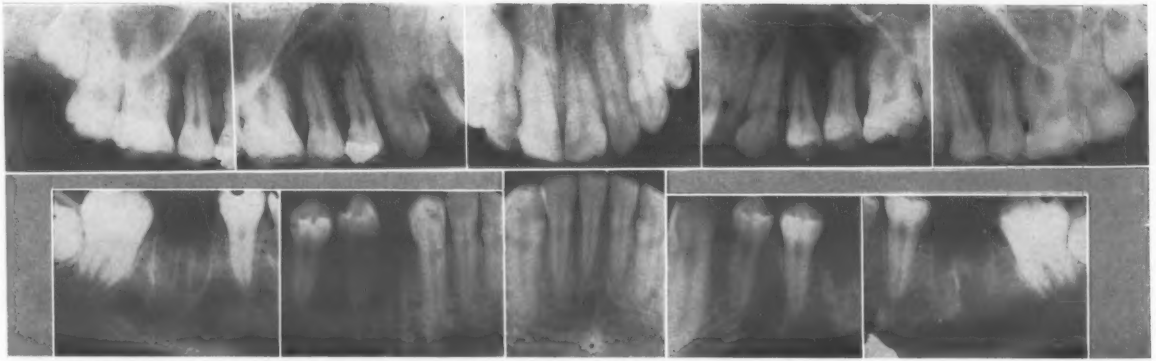


Fig. 2.—Case 1. Roentgenogram taken in May, 1935. Note the cystlike areas in the molar and premolar regions and absence of well-defined wall as seen in true cysts. Lamina dura and periodontal membrane are intact and sharply outlined. Porosity of bone is well exemplified in the region extending from canine to molar areas. The maxillary premolar area shows regions of osteolysis.

Fig. 3.—Case 1. Roentgenogram of left jaw, taken in June, 1936. Note the spotty areas of decalcification with loss of trabecular structure in the premolar zone. Note thinning of the bone cortex.

no complicating hemorrhagic phenomena are present. Often there is bleeding from the gingivae and nose with spontaneous hemorrhage from the mucous membranes of the mouth. Several authors have described an inconstant but easily recognizable symptom—a brownish yellow wedge-shaped thickening, affecting first the nasal side of each conjunctiva, its base being limited by the cornea. Later, the temporal side also becomes involved with a similar thickening. This sign is present in only about 15 per cent of the cases and is often spoken of as pinguecula. This was noted in only one out of six cases. In most instances, bone lesions of the disease have led to the diagnosis.

Bones appear less radiopaque because of their extreme porosity; cancellous bone is coarse grained and "worm-eaten" in appearance and, in addition, may show large pseudocystic defects and noticeable thinning of the cortex. Collapse and deformity of the femur are visible in the roentgenogram, and a clublike or Erlenmeyer-flask appearance of the lower portion of this bone is often evidenced. This sign is considered pathognomonic if it is present. Usually there is destruction of the spongiosa with marked loss of trabecular structure. The bone cortex and the periosteum can be involved. The skull changes in this disease, as contrasted with Schüller-Christian disease, are minimal. Spontaneous fractures occur frequently, and healing follows standard orthopedic therapy. Regenerative changes in the bones are often observed, and in some instances these changes have been erroneously attributed to splenectomy. Long follow-up studies reveal renewed degenerative changes exhibiting even more extensive bone lesions in many cases.

The following report describes osseous dysplasia in Gaucher's disease, with manifestations in the bones of the jaw in five of six observed cases. A twenty-year follow-up exhibiting changes in dental films in two cases reported[1] earlier is presented.

CASE 1.—A Jewish girl, aged 13 years, presented herself in May, 1935, to have two lower first molars extracted. The soft structures of the mouth revealed no abnormalities. An x-ray examination after extraction (Fig. 2) showed areas of marked radiolucence, especially in the molar and premolar zones, with a pseudocystic appearance. A nest of cells or cysts seemed to have a foamy appearance, and a few strands of bone structure were noted to be present within the cells. The mental region of the mandible presented a slight generalized porosity. Areas of lysis were observed in the upper premolar area. Lateral jaw films revealed a loss of trabecular structure, especially in the mandibular molar and premolar areas (Fig. 3). The history revealed that the patient was treated for osteomyelitis of the tibia and underwent a splenectomy in February, 1933, because of Gaucher's disease. A study of her old roentgenograms revealed similar trabecular destruction in the skeleton. The diagnosis of the Gaucher lesions in the mandible was based on a priori diagnosis. Dental films were again taken in 1936 (Fig. 4). There was some evidence of bone healing, which was erroneously attributed to the splenectomy. It may have been a result of a remission of the disease or it may have been due to the extractions. The osteomyelitis complication continued for eight years, until the patient was finally cured with penicillin and orthopedic surgery. During this entire period following splenectomy the patent finished school and was gainfully employed, and her activities were not limited. She received supportive therapy for her anemia. She married and became pregnant in 1946. During her third month of pregnancy, she developed a spontaneous hemorrhage in the region of the hard palate. This was arrested by electrocoagulation. A blood study indicated a reduction

Fig. 4.

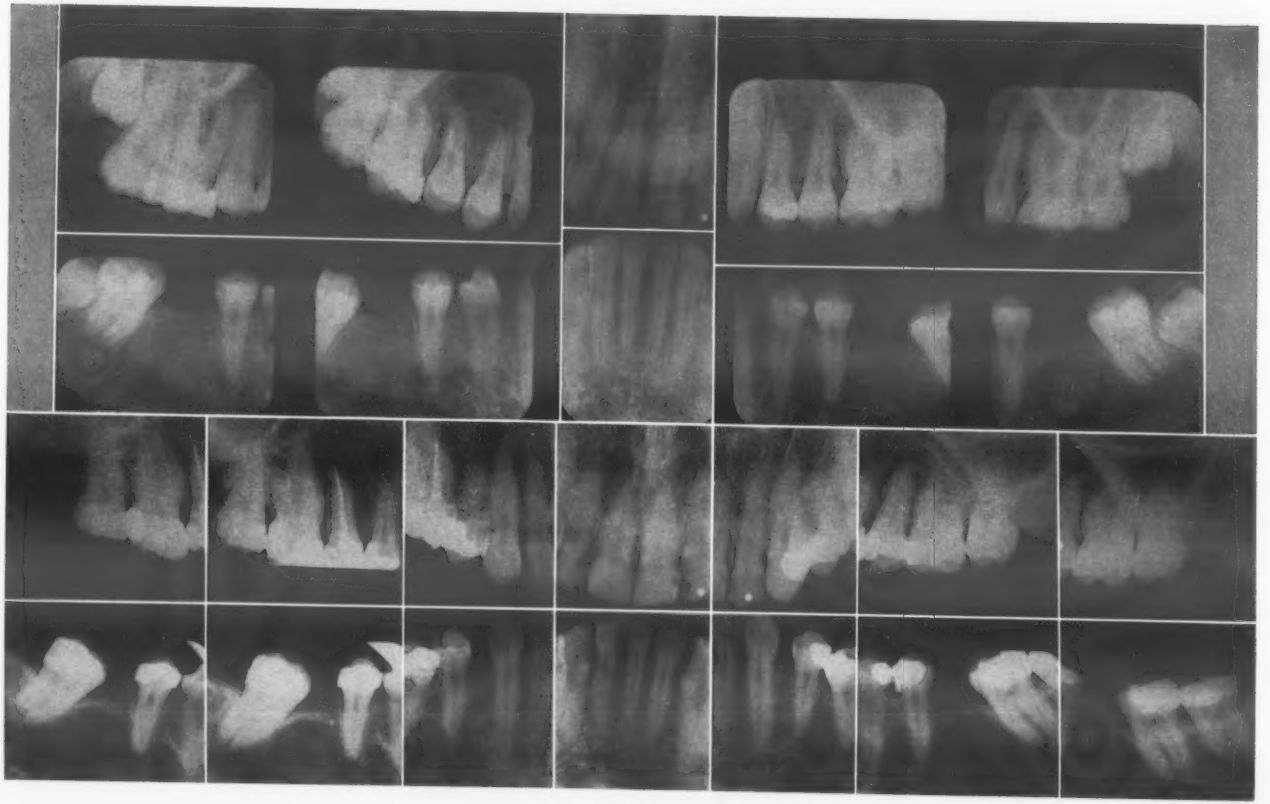


Fig. 5.

Fig. 4.—Case 1. X-ray examination made in 1938 reveals some evidence of bone regeneration. This may be due to a remission of the disease or to extraction of the first molars.

Fig. 5.—Case 1. Dental films taken in June, 1948. Note the marked loss of trabecular structure in the molar and premolar region on both sides of the mandible, as compared with films taken in 1938. There is definite evidence of root resorption of the right mandibular second premolar and molar. There is increased porosity throughout both the mandible and the maxilla, with a pseudocystic appearance in the mandible.

in the blood platelets. Two weeks later another spontaneous hemorrhage occurred, and this too was treated by electrocoagulation. In view of these findings, a therapeutic abortion was performed. About 1949, two years after the foregoing episode, the patient, upon walking, developed a spontaneous fracture of the right femur. She was confined to bed for almost nine months. She made a good recovery and is now walking very well. She and her husband have adopted a baby and are happily leading normal, healthy lives.

Dental films taken in 1950 revealed more extensive areas of radiolucency in the mandible than were observed in 1936 (Figs. 5 and 6). The latest films, taken in 1956, show no evidence of any increase in the bone lesions of the mandible as compared with 1950 (Fig. 7).

Fig. 6.—Case 1. Roentgenograms taken in 1956. Note the pseudocystic appearance with an increased loss of trabecular structure in the molar and premolar region, with thinning of the bone cortex. Compare with Fig. 3.

Case 2.—In 1935 a Jewish woman, aged 27 years, presented herself for x-ray examination at the Jewish Hospital for possible fracture of the left humerus. The roentgenogram revealed a fracture with unusual osseous changes. The patient was hospitalized for further studies. Physical examination revealed no abnormalities and no splenic or liver enlargement. A hemogram revealed a hypochromic anemia and a slight thrombocytopenic purpura. Blood calcium was 10 mg. per 100 ml. of blood; blood phosphorus was 4.7 mg. per 100 ml. of blood; blood cholesterol was 147 mg. per 100 ml. of blood; a Bence Jones protein bodies test was negative. Roentgenograms revealed involvement of both humeri. The right humerus showed small areas of lysis, irregularly distributed throughout the cortex and medulla. There was evidence of destruction of the periosteum. This was somewhat similar in appearance to multiple myeloma. About the distal portion of the shaft of the bone was some medullary widening, and this was accompanied by a thinning of the cortex. The lower end of the humerus had a trabeculated appearance. In the shaft of the humerus, the usual transverse bone trabeculae were not seen. In addition to these changes, there were other lesions in other parts of the skeletal system, especially in the femurs.

Dental examinations revealed no abnormalities in the soft structures. Dental films revealed a generalized porosity in the mental region. Areas of bone lysis with loss of trabecular structure were noted in the right and left mandibular molar and premolar areas. There was a generalized porosity and demineralization, in both the maxilla and the mandible (Fig. 8). These changes supported a tentative diagnosis of Gaucher's disease. A biopsy of the bone cortex of the right humerus confirmed the diagnosis of Gaucher's disease.

There was no definite evidence at this time that the lesion in the mandible was due to Gaucher's disease. It was only presumptive evidence in that the lesion in the mandible

Fig. 7.—Case 1. Roentgenograms taken in June, 1956. There is not much difference in appearance as compared with the 1948 study. Note the moth-eaten and foamy appearance in the pseudocystic areas of the molar region.

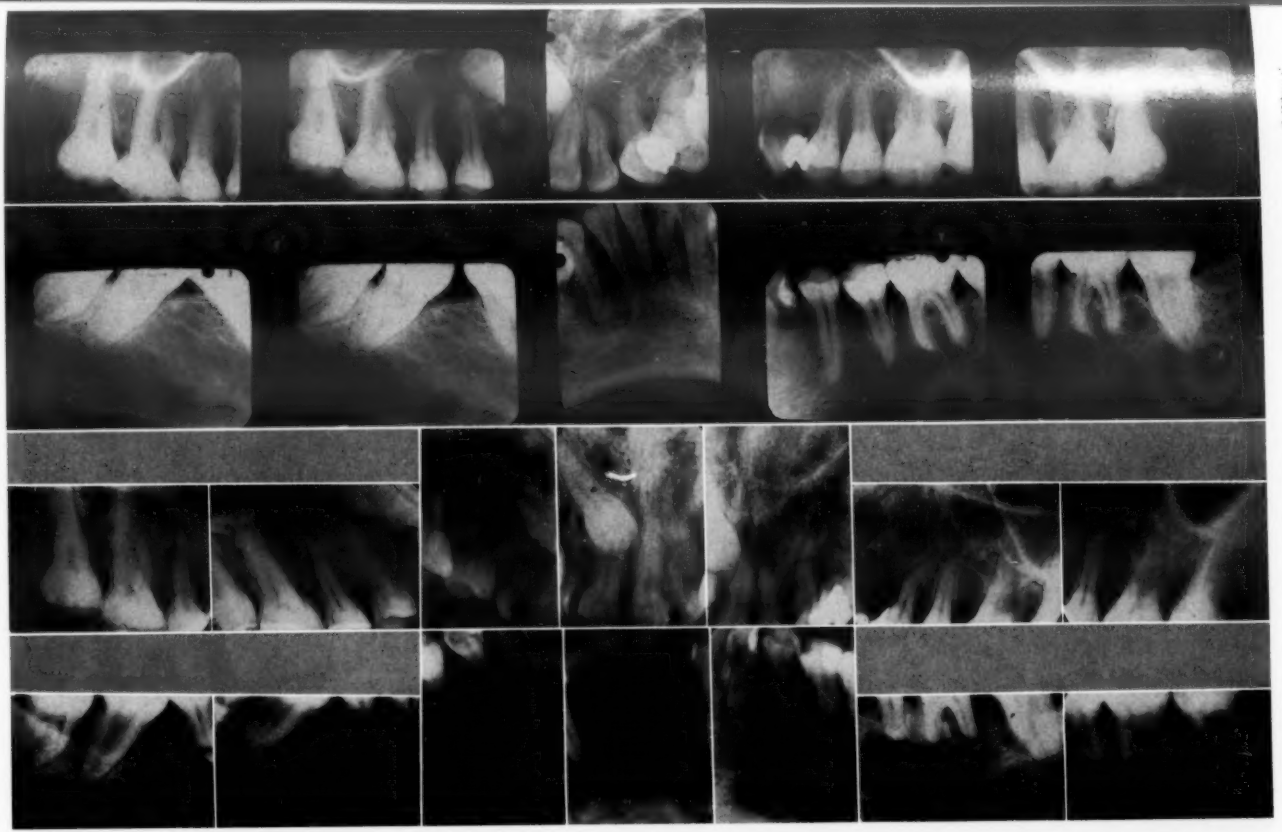


Fig. 9.

Fig. 8.—Case 2. Roentgenograms taken in 1935. Note the porosity in the mental region. The molar and premolar zones show large areas of rarefaction with strands of bone tissue, pseudocystic in appearance, still intact. The bone of right lower molar area and the entire maxillary region exhibits marked trabeculation on both sides. The region of the upper premolars shows an area of lysis. The possible infiltration of Gaucher's cells is beginning to show the effects of pressure, producing root resorption of the first molar and second premolar.

Fig. 9.—Case 2. Roentgenograms taken in 1945. The trabeculae are thinner and larger throughout, and there is marked loss of trabecular structure, particularly in the region of the mandible. Note the extent of the destruction of bone on both sides in the molar and premolar areas as it extends to the region of the canine. There is evidence of a "moth-eaten" appearance, especially in the left molar area. Note the evident increased root resorption in the left mandibular molar and premolars and some root resorption in the second molar and right mandibular posterior teeth. This may be the result of the increased infiltration of the Gaucher cells.

was the same as the lesion in the humerus. The patient was then seen in 1945, and dental films revealed an increased porosity with more extensive areas of radiolucency and marked loss of trabecular structure in the molar and premolar areas of the right and left mandible. There was manifested within the radiolucent areas a "worm-eaten" cystic appearance. There was evidence that the pressure of the infiltrating foam cells was producing a resorption of the roots of the right lower first molar and premolars, and the lesion was beginning to infiltrate into the bone cortex. Thinning of the cortex in both the right and left sides of the mandible and extensive alveolar resorption were present (Figs. 9 and 10). Clinically, periodontoclasia was present and the patient was advised that her teeth would have to be extracted in the very near future. In April, 1947, a blood study displayed a moderate macrocytic anemia, leukopenia, and a thrombocytopenia with a platelet count of 72,000. Sternal biopsy puncture revealed Gaucher's cells and a hyperplastic marrow with abnormalities in maturation of erythroid and megakaryocytic elements. These abnormalities could be caused by infiltration of the marrow with lipoid-laden histiocytes. Bleeding time was one and one-half minutes, and clotting time was two minutes. Physical examinations revealed a slightly palpable spleen.

Fig. 10.—Case 2. Roentgenograms taken in 1945. Lateral jaw film shows the extent of the loss of the trabecular structure, root resorption, and the marked thinning of the cortex. (Courtesy of R. S. Shira.)

In May, 1947, all of the patient's teeth were extracted, and a tumor mass was curetted from the right and left sides of the mandible. The tumor proved to be solid and very friable. There was no evidence of any cyst formation. The removal of teeth and of the tumor mass was followed by hemorrhage with marked ecchymosis of the neck and chest.

Pathologic Report.—The specimen consisted of numerous fragments of light brown semifirm tissue and dark brown hemorrhagic tissue, making an aggregate mass approximately 2 cm. in diameter. Several of the pieces contained small spicules of cortical bone. A singular large spicule of cortical bone was embedded.

Microscopic examination: Sections showed fragments of dense cortical bone with fibrosed marrow spaces and canaliculi. The bulk of the tumor tissue was composed of lipoid-laden histiocytes with areas of fibrous connective tissue. No new bone formation was seen within the tumor proper. In places, bone marrow elements were still present. Spicules of partially resorbed bone trabeculae were seen. The process was characterized by osteolysis,

by the presence of Gaucher's cells, and by the formation of fibrous connective tissue. There was no evidence of any malignancy, adamantinoma, cyst formation, or fibrous dysplasia. *Diagnosis:* Gaucher's disease (Fig. 11).

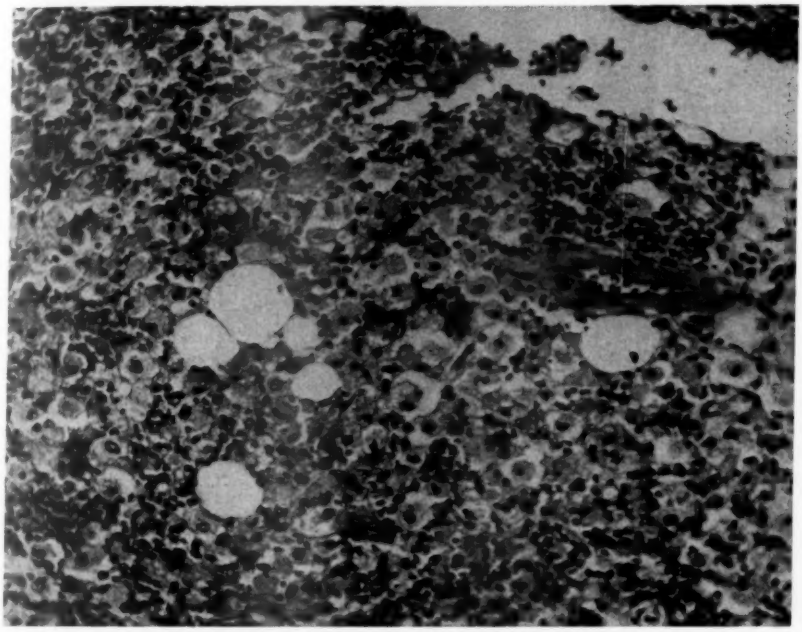


Fig. 11.—Case 2. Biopsy specimen. Most cells possess one small, round nucleus; a few are multinucleated. (Courtesy of R. S. Shira.)

Fig. 12.—Case 2. Roentgenograms taken in 1947. Lateral jaw film after surgery shows the regeneration of the cancellous portion of bone. (Courtesy of R. S. Shira.)

Full upper and lower dentures were inserted in July of the same year. In September, 1947, roentgenograms (Fig. 12) of the edentulous areas revealed evidence of bone regeneration in the body of the right and left sides of the mandible. Intraoral films taken in 1955

Fig. 13.—Case 2. Roentgenograms taken in 1955. Note the condition of the bone now. There is again evidence of loss of trabecular structure with distinct evidence of a "moth-eaten" appearance in the region of the mandible. The lower left molar region manifests a cystic lesion that is encroaching on the mandibular cortex.

(Fig. 13) revealed evidence of redeposition of Gaucher's cells, causing a porosity of the cancellous bone with a "worm-eaten" appearance. The patient is well, and her activities are not limited. In the latter part of 1955 she had a skiing accident and fractured her tibia, which responded to standard orthopedic procedure. So far, the spleen has not been removed.

DISCUSSION

Since my report of the first three cases of Gaucher's disease,[4] three others have been reported in the literature. The one reported by Shira,[5] unbeknown to him, was the same patient (Case 2) reported by me. Shira confirmed the presumptive diagnosis of Gaucher's disease with a bone biopsy from the mandible. Moch[6] reported the fourth case with definite histologic evidence of the disease in the mandible. Spiegel[7] reported the fifth case on a priori evidence. With one exception, the five cases reported and three others that I have seen all showed bone changes in the mandible, and to some extent in the maxilla. In the one case that did not show such changes, the patient, a 9-year-old boy, did have bone changes in the region of the head of the femur.

In Gaucher's disease definite bone lesions are present in the mandible with a loss of trabecular structure, particularly in the molar areas. However, areas of radiolucence are often encountered under normal conditions in these areas. Lateral jaw films often help to delineate the pseudocystic areas showing the extent of the loss of the trabecular structure and thus aid in differentiating the normal from the abnormal. All the cases that have been reported so far have shown bone changes in the mandible.

Cahn's[8] point is well taken when he states that "large bilateral radiolucent areas in the mandible may represent deposits of hematopoietic marrow." But in this disease other dental signs are observed: (1) There is a generalized porosity of the mandible and the maxilla, with loss of the trabecular structure. (2) There is a pseudocystic radiolucent area in the molar and premolar regions, with a "worm-eaten" appearance. (3) Sometimes there is porosity in the mental region. (4) There is a thinned-out mandibular cortex. (5) Areas of osteolysis may be present in the maxillary premolar areas. (6) Root resorption may take place as a result of the infiltration of Gaucher's cells. This is usually seen in the later stages of the disease. (7) Bone regeneration follows curettement of lesions or extractions. (8) Degeneration with loss of trabecular structure and "worm-eaten" appearance occurs after regeneration, because of a renewed deposition of the kerasin-laden cells.

While a biopsy is most desirable to establish a definite diagnosis in the mandible, a priori or presumptive diagnosis is permissible if it has been established in another part of the skeletal system. Biopsy specimens cannot be taken from all over the body just because one group is interested in the jaws, while another is interested in the skull and still another in the long bones. It is doubtful that two different diseases that produce bone lesions can exist simultaneously. Moreover, all the cases that were reported on an a priori basis exhibited laboratory and clinical evidence of the disease with distinct bone changes.

The problem of surgery in Gaucher's disease is fraught with some degree of danger because of hemorrhagic complications. This is true especially in patients who have not had a splenectomy. The blood changes—namely, anemia, leukopenia, and thrombocytopenia—usually disappear following splenectomy.

Fig. 14.

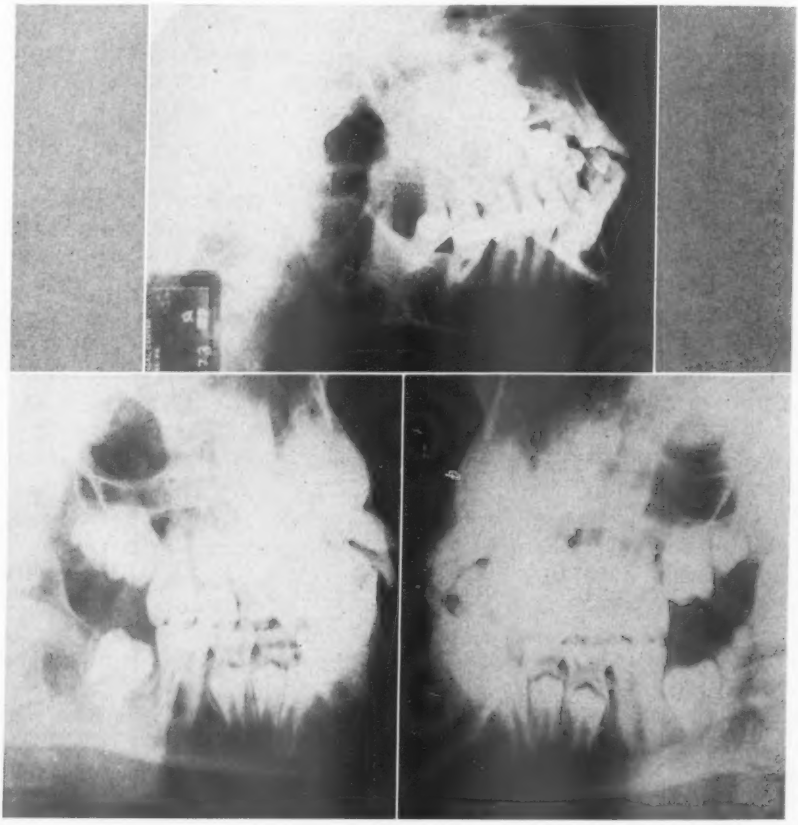


Fig. 15.

Fig. 14.—Another case showing the typical Gaucher's disturbance in the region of the mandible in a 52-year-old patient. Distinct lesions are also present in the other parts of the skeletal system. The diagnosis is based on prior evidence established by removing a portion of the upper end of the humerus.

Fig. 15.—Another case exhibiting evidence of Gaucher's disease in a 12-year-old boy. The right and left sides of the mandible show loss of trabecular structure in the molar and premolar area. There is evidence of thinning of the cortex. (Note the markedly enlarged spleen in this case as illustrated in Fig. 1.) (From Tassman, G. C., and Bender, I. B.: J. Am. Dent. A., August, 1940.)

This is followed by a rise to 10,000 or 12,000 in the white cell count and an increase in the blood platelet count which in some cases may reach as high as 1,000,000 platelets. After a number of years, however, the thrombocytopenia

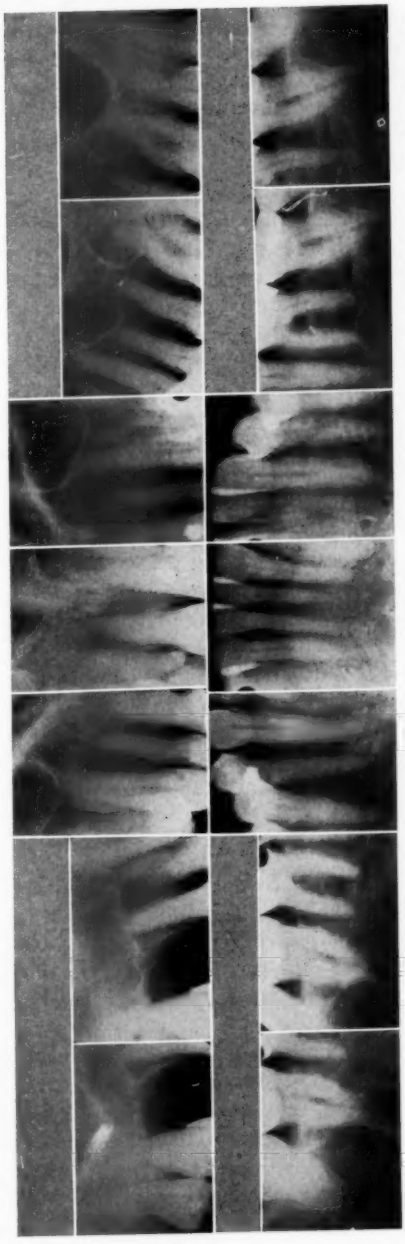


Fig. 16.—Intraoral roentgenograms exhibiting early bone changes in the region of the mandible in another case of Gaucher's disease.

and the anemia may return as a result of the increased Gaucher cell infiltration, as occurred in the first case. If any surgery has to be performed, it is best to consult with a hematologist for proper evaluation of the patient.

Of the four cases reported in which oral surgery was performed, only one did not have hemorrhagic complications, and this patient had undergone a splenectomy. The three patients who did not have splenectomies all had episodes of prolonged bleeding. In the case reported by Moch, blood transfusion was required in order to arrest the hemorrhage; the patient operated on by Shira had marked hemorrhage and ecchymoses, while Spiegel's patient had a marked oozing of blood following surgical removal of a third molar tissue flap.

The twenty-year follow-up study revealed that the bone lesions can increase in size. The increase, however, takes a number of years and may not manifest itself in a short period of one to two years. The increase in the kerasin deposition may produce resorption of the roots as a result of the increased pressure on the root ends. It was also observed that surgery or curettement of the involved lesions produces a regeneration of bone with evidence of healing. This is followed later by a porosity caused by redeposition of Gaucher's cells, giving the bone the typical "worm-eaten" appearance. Periods of remission of the disease with changes in the hemogram are also observed.

The thinning of the bone cortex of the mandible was one of the most consistent findings in both the early and late stages of the disease. The degree of the bone changes does not necessarily reflect early or late stages of the disease; rather, it indicates the intensity or degree of the metabolic rate of the disease. Patients may have this disease for many years and show only minor changes, while in others the disease can be more rapidly progressive with manifestations of a hemorrhagic diathesis.

Gaucher's disease is another example of a systemic disorder that can be detected by means of dental x-ray, particularly since it is chronic in its course and bone lesions may be present even before splenic enlargement develops.

SUMMARY

Dental observations in eight cases of Gaucher's disease are described. In seven cases there were lesions in the mandible, the maxilla, and other parts of the skeletal system. One patient did not have any osseous dysplasia in the jaws when examined but did show changes in the femur.

Two of the five cases that are described were followed for a period of twenty years.

In one of these cases a biopsy of the mandible was performed to confirm the original presumptive diagnosis based on a biopsy from the humerus. The biopsy and diagnosis were confirmed by another observer.

Both cases exhibited a slow, gradual enlargement of the original lesions observed in the early stages of the disease.

Lesions manifested evidence of bone regeneration following surgical interference. This was later followed by a reappearance of loss of trabecular structure with a "worm-eaten" appearance of the mandible.

One of the cases developed a spontaneous hemorrhage of the palatal mucosa.

All the cases exhibited a loss of trabecular structure with a pseudocystic appearance in the molar and premolar areas of the mandible. A thinning of the bone cortex of the mandible was a constant finding. In the later stages of the disease, infiltrating Gaucher's cells can produce root resorption.

Other intraoral x-ray changes, which have been confirmed by two cases reported in the literature, are described. Hemorrhagic complications following oral surgery are discussed. The dental findings in Gaucher's disease may have some diagnostic significance.

REFERENCES

1. Epstein, E., and Lorenz, K.: Ztschr. f. physiol. Chem. **192**: 145, 1930.
2. Lieb, H.: Ztschr. f. physiol. Chem. **115**: 305, 1924.
3. Bender, I. B.: Dental Observations in Gaucher's Disease, J. D. Res. **17**: 359, 1938.
4. Tassman, G. C., and Bender, I. B.: Gaucher's Disease: Case Report, J. Am. Dent. A. **27**: 1268, 1940.
5. Shira, R. S.: Manifestations of Systemic Disorders in the Facial Bones, J. Oral Surg. **11**: 286, 1953.
6. Moch, Walter S.: Gaucher's Disease With Mandibular Bone Lesions, ORAL SURG., ORAL MED. & ORAL PATH. **6**: 1250, 1953.
7. Spiegel, Lewis H.: Gaucher's Disease, ORAL SURG., ORAL MED. & ORAL PATH. **10**: 158, 1957.
8. Cahn, L. R.: Comment on Moch.[6] ORAL SURG., ORAL MED. & ORAL PATH. **6**: 1253, 1953.

1551 CHAMPLOST AVE.

ORAL ROENTGENOLOGY

American Academy of Oral Roentgenology

Arthur H. Wuehrmann, Editor

THE FUNDAMENTAL BIOLOGIC EFFECTS OF X-RAYS IN DENTISTRY

Lincoln R. Manson-Hing, D.M.D., Birmingham, Ala.*

Soon after the x-ray was discovered by Wilhelm Konrad Roentgen in 1895, there were reports of erythemas, dermatitis, and ulcerations resulting from x-ray absorption. With the turn of the century there were reports of neoplastic changes in tissues brought about by exposure to x-rays. Many dentists who were ignorant of the early warnings or chose to ignore them suffered the loss of one or more fingers due to the then common habit of holding the film in the patient's mouth and thus exposing the fingers to repeated doses of x-radiation. The days of such ignorance are over, and standards for protection have been set up. These standards, however, are likely to be revised as new information on the biologic effects of radiation upon man becomes available.

X-rays have been used in dentistry since the early x-ray tubes were manufactured; today x-ray machines specially designed for oral roentgenography are available to the dental profession. The techniques of good oral roentgenography and the safe handling of x-radiation in dentistry are adequately covered in recent dental literature, but information about the biologic effects of these radiations is not as readily available to the average dentist. There is the feeling among many dentists that one cannot understand the changes brought about in human beings by the exposure to x-radiation without extensive knowledge in the fields of physics, chemistry, and mathematics. This is true only if one wishes to become a radiobiologist; such knowledge is not necessary if the dentist wishes merely to have a practical understanding of this subject.

The purpose of this article is to present a concise but elementary description of the biologic and pathologic effects of x-radiation and the concepts

*Assistant Professor of Dentistry, University of Alabama, School of Dentistry; member of the American Academy of Oral Roentgenology.

that should be understood by the dentist. The material presented here is of such a general nature that numerous references can be found in scientific literature. Specific references are therefore omitted from this article. However, for those who wish a better understanding of the subject, a list of references (books and articles pertinent to this discussion) is included at the end of this article. It is felt that a better understanding of the biologic effects will be obtained by the uninitiated dentist from a discussion of these effects at various levels. The levels used in this article separate the various biologic effects into those which affect the molecules, the body chemistry, the cells, the tissues, the whole body, the genetic material, and whole populations. The effects seen at a later level, such as those appearing in tissues, cannot be fully appreciated without some idea of what happens at the lower levels of the molecules and cells. The reader will note that the effects on the genetic material have been dealt with under a separate heading, although these effects occur at the cellular level. The reason for this approach is that the genetic effects of x-radiation and their implications are of paramount importance to the dental practitioner. A description of the effects occurring at the various levels is given with as brief an explanation as possible. It is hoped that presenting the material in this manner will enable the reader to obtain an over-all picture of the effects of x-ray absorption by human beings.

IONIZATION—THE MOLECULAR EFFECTS OF X-RADIATION

X-radiation belongs to the family of electromagnetic radiations and is one of the many forms of ionizing radiation. It consists of single discrete units called photons or quanta, and although considered to have a wave form, it exhibits many of the properties of a particle. The wave length of a photon is measured in Angstrom units; the shorter the wave length, the more energy the photon possesses. The wave lengths of x-rays are much shorter than those of visible light; for that reason, these photons possess the ability to penetrate matter. All matter is made up of atoms. An atom consists of a centrally located nucleus with a positive electrical charge around which one or more electrons with a corresponding total amount of negative electrical charge travel in different orbits. There is a void between the electrons and the nucleus. When any of the photons used in dentistry reaches an atom or molecule, one of three things can occur: It can pass right through the atom without any change; it can hit the nucleus and change its direction without any change in the atom or photon except for a resulting photon of scattered radiation; or it can hit an orbital electron and dislodge it. The removal of these electrons from their orbits by x-rays results in an atom that now has a positive electrical charge and a dislodged electron with a negative charge. These two things are often referred to as an ion pair. The free electron soon ties up with an atom or molecule, resulting in that atom or molecule now possessing a negative electrical charge.

X-rays having energies like those used in dentistry will dislodge electrons from their orbits in two ways. First, the entire photon can be absorbed by

the electron, resulting in the disappearance of the photon and in the production of an electron called a photoelectron which travels at a high rate of speed. This photoelectron now collides with the electrons of other atoms, dislodging them from their atoms while losing some of its energy; thus, the end result is the production of many ion pairs. Second, the photon can dislodge an orbital electron and lose some of its energy; the result is a high-speed electron and a photon which now has less energy and thus a longer wave length. The high-speed electron has properties identical to those of a photoelectron and, like the photoelectron, it creates ion pairs while giving up its energy. In colliding with the electron, the photon is changed in its direction and now becomes a photon of scattered radiation. Of these two mechanisms of photon absorption, the first is much more frequently the mode of action for x-rays generated by dental x-ray machines.

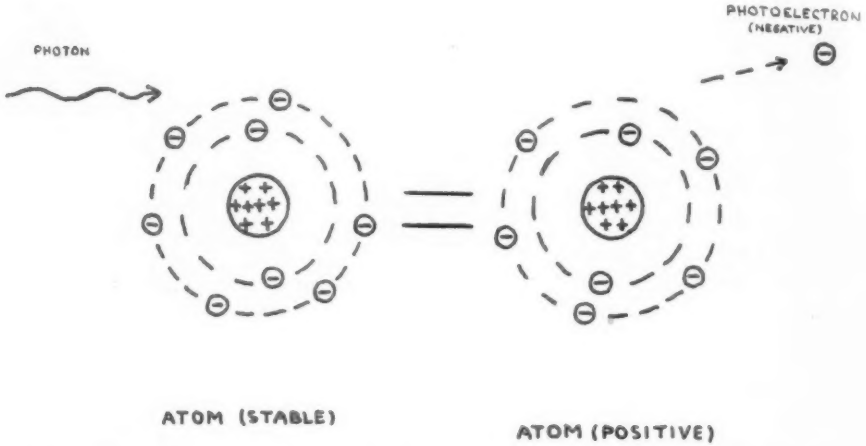


Fig. 1.—Diagrammatic representation of the absorption of an x-ray photon by an atom producing an ion pair.

The orbital location of the electron that is removed is important. It has been stated that the atom consists of a nucleus and one or more electrons orbiting around it at different levels or shells. If an electron in the outermost shell is removed, the atom now has a positive electrical charge and remains unchanged until it comes in contact with a negatively charged atom or electron. If an electron in one of the inner shells is dislodged by the photon, however, an electron in a higher shell will fall in to take its place. When this outer electron moves to an inner shell, it will give up energy in the form of an x-ray photon, the wave length of which is characteristic of the element to which that particular atom belongs. These characteristic radiations are emitted in all directions, adding to the scattered radiation problem; the atom still possesses a positive electrical charge.

It is clearly seen that the absorption of x-rays results in the production of many ion pairs. These ion pairs may consist of positively charged atoms and negatively charged electrons or positively charged atoms and negatively charged atoms.

CHEMICAL EFFECTS OF X-RADIATION

The structure of a molecule is brought about by the linking together of various atoms by chemical bonds. This is made possible by the sharing of electrons between the atoms joined together. The removal of the shared electron leads to the separation of the joined atoms. The removal of other electrons will also lead to separation of the joined atoms, since the energy involved in this type of ionization is enough to cause the separation. Another way of separating joined atoms with x-radiation is by *excitation*. Here, the electron absorbs the photon without being ejected from its orbit; the electron is raised to a higher energy level, and this results in the separation of the joined atoms. The longer electromagnetic waves, such as ultraviolet and visible light, are also capable of creating ion pairs by this method. Irradiation of tissue results in the formation of many different radicals consisting of positively and negatively charged atoms or molecules and electrons. Recombination of these various radicals can produce all kinds of new chemicals. The type of radical produced during the irradiation of any one chemical may vary with the form that it is in at the time of irradiation, such as a gas, a liquid, or a solid, and also with the presence of certain other elements.

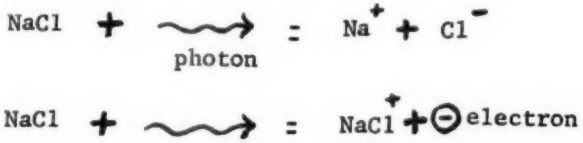


Fig. 2.—Equations showing two simple reactions achieved by irradiation. The first one shows the usual chemical separation by excitation of sodium chloride (common salt) into a positive sodium and a negative chloride ion. The second shows the production of an ion pair consisting of a positively charged sodium chloride molecule and an electron.

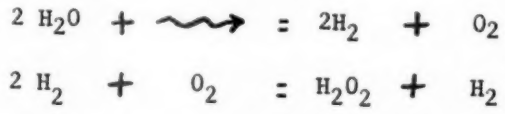


Fig. 3.—Equations showing one of the possible ways in which hydrogen peroxide is formed when water is exposed to x-radiation.

The equations in Figs. 2 and 3 show basically how some radicals are formed by x-radiation and how new chemicals, foreign to the human body, may be produced. Obviously, this field is extremely difficult to investigate, and therefore the effects of radiation upon the biochemistry of the body cannot be well evaluated at this time.

EFFECTS OF X-RADIATION UPON CELLS

The effect of x-radiation upon cells can be classified as indirect or direct. The indirect form may be the deactivation of enzymes or hormones. Another indirect mode of action may be through the production of cell poisons made during the irradiation of proteins in other cells. These poisons may be carried away from the site of origin and, upon reaching the normal cell, cause its death.

The direct action of x-rays on the cell may cause changes within the cell in ways similar to those of indirect action and in other ways as well. The direct action of x-radiation on viruses which seem to be made up of large protein molecules can result in the deactivation of these viruses. In higher cells this action on the protein within the cell may be a possible mode of action that could result in disruption of the cell's chemistry and ultimately lead to the death of the cell.

One of the most important effects seen at the level of the cell is the damage done to the chromosomes by x-radiation. Microscopically, the chromosomes appear like strands or strings. It is believed that the genes, or factors controlling the cell, are located like beads along these chromosomes. The effect of x-rays upon these chromosomes can be the loss of a gene or a mutant change in a gene (called a "point mutation"). The implication of such changes in a somatic cell is that the cell may now exhibit an abnormal pattern of behavior. The results of such changes in a genetic cell are discussed later in connection with the genetic effects of x-radiation. The effect of x-rays upon the chromosomes can also result in the breaking of one or more chromosomes. The broken ends of the chromosome seem to possess the ability to join together again after separation. If the separation is great, the chromosome may lose part of its structure. There may be more than one break in one or more chromosomes, resulting in a great variety of recombinations. Illegitimate unions, in which a section of one chromosome joins up with a section of another broken chromosome, have been observed.

Cells exhibiting chromosomal breaks tend to survive until they attempt to divide; the result at this time is usually death of the cell. This phenomenon, therefore, results in a tendency for the more rapidly dividing cells to show damage after irradiation. It also gives one explanation for the successful use of x-rays in the treatment of rapidly growing tumors even though the x-rays themselves are carcinogenic.

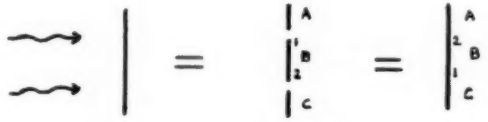
X-radiation exhibits a special effect upon cell division apart from that shown through damage to the chromosomes. This effect upon cell division is one of arrested mitosis; the extent of the interference varies with the stage of development that the cell is in at the time of irradiation. The most important effect is that cells in the prophase stage of mitosis are arrested in their progress toward division. This delay is so great that another irradiated cell starting division after it may well succeed in dividing into two cells before the arrested cell completes its cycle. Endomitosis is another effect which x-rays may have upon cell division. Here there is duplication of the chromatin within the cell without the cell dividing into two separate cells. In general, it can be said that cells undergoing mitosis are most susceptible to x-radiation.

Briefly, then, it can be demonstrated that x-radiation can produce chromosomal damage, arrested mitosis, endomitosis, impaired function, and the death of the cell. It may be of interest here to note that many of these changes can also be produced by certain chemicals (for example, nitrogen mustard).

EFFECTS OF X-RADIATION UPON TISSUES

Tissues vary in their reaction to x-rays. Tissues can be regarded as groups of cells, and it has been stated previously that cells undergoing mitosis show an increased susceptibility to x-radiation. Generally speaking, tissues that are growing rapidly or constantly replacing their cells through mitosis show greater damage from the same dose of x-radiation than tissues that have little or no mitotic activity. Thus, the tissues of the body can be divided into two broad groups of radiosensitive and radioresistant tissues.

Simple loss of a part of a chromosome due to x-radiation



Breakage of a chromosome into 3 parts with inversion of the B segment upon rearrangement

Fig. 4.—Diagrammatic representation of two simple chromosomal breaks that can be caused by x-rays.

The radiosensitive group, starting with the most sensitive tissue, consists of (1) blood-forming tissues, (2) reproductive cells, (3) lymphatic tissues, (4) young bone tissue, and (5) skin. The radioresistant group, listed in decreasing order of sensitivity, consists of (1) most glandular tissues, (2) muscle tissue, (3) nerve tissue, and (4) mature bone tissue. It must be borne in mind that not all the cells of a tissue are affected by a beam of x-rays. Most of the cells will show no injury whatsoever, but a few will be killed and a few will show either permanent or transient injury.

Tissues do not always react immediately to a dose of x-radiation. There is a time lapse before any effects are seen; this is referred to as the latent period. This latent period varies with the quality of the x-rays used to produce ionization of the tissue. Generally speaking, the latent period increases as the wave length of the x-rays used decreases; in other words, the latent

period increases as more penetrating x-rays are used. The existence of this latent period explains why injuries from small doses of x-radiation sometimes do not become evident until months or even years have passed since the time of absorption of the x-rays. There are physical factors which vary the tissue dose and thus the tissue response to x-radiation; some of these will be discussed later.

The cumulative effect of repeated doses of x-radiation is of interest to the dental profession. When tissues are irradiated, the amount of reaction will depend greatly upon the dose delivered. Whatever this reaction is, there will be repair to the damaged tissues as long as complete degeneration has not occurred. The tissues do not return to their original state, however, as there is some irreparable damage and this irreparable damage is what is cumulative. This is shown diagrammatically in Fig. 5.

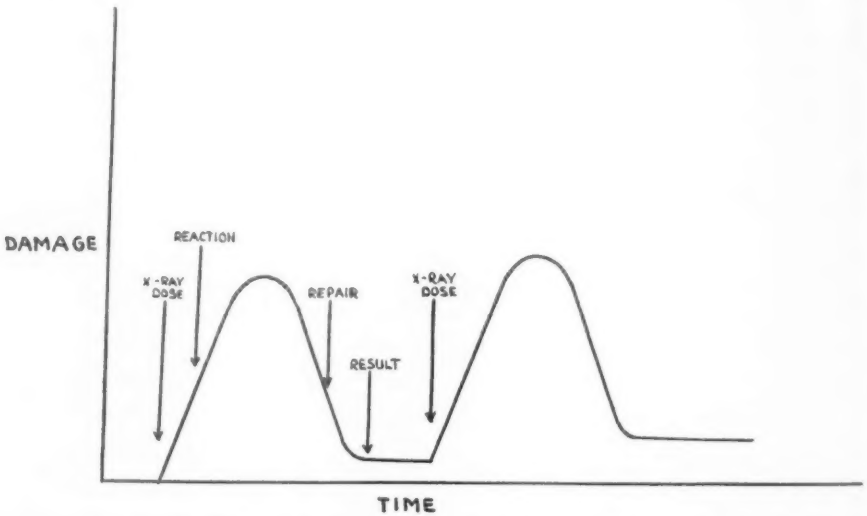


Fig. 5.—Diagrammatic representation of the cumulative effect of x-radiation.

Tissue absorption of x-rays results in a multitude of effects. The result is dependent upon a variety of factors, some of which have already been discussed. The practicing dentist can think of x-ray absorption as producing in tissue a sequence of events such as the following: (1) erythema, (2) chronic dermatitis, (3) atrophy of the skin with loss of hair and glandular structures, (4) hyalinization of collagen, (5) damage to immature blood cells with leukopenia and leukocytosis, (6) endarteritis obliterans with fewer smaller arteries, (7) ulceration, (8) osteoradionecrosis, and (9) mutations with neoplastic activity.

The most important stage of tissue reaction to be recognized by the dentist is that of x-ray dermatitis. The dentist and his patients are more

prone to receive repeated small doses of x-radiation, and the first clinical indication of any damage done by x-rays administered in this manner is the appearance of a chronic dermatitis. The visible manifestations of x-ray damage to the hands or skin can be divided into early and late symptoms. The early signs can be described as (1) increased susceptibility to chapping and an intolerance to surgical "scrub-up," (2) blunting and leveling of the finger ridges, and (3) brittleness and ridging of the fingernails. The late signs can be described as (1) loosening of the hairs and epilation, (2) dryness and atrophy of the skin, and (3) progressive pigmentation or tanning of the skin.

Osteoradionecrosis is another stage of tissue effects that is important to the dentist. Osteoradionecrosis resulting from radiation alone is not seen in the dental office, as this usually occurs from an overdose of radiation during radiotherapy. However, persons who have had radiotherapy have a marked predisposition to this condition in the area that has received therapy. Most malignancies within the oral cavity show relatively little increased radiosensitivity when compared to their tissues of origin. It is to be expected that when these malignancies are treated by ionizing radiations the normal tissues within the beam of radiation will receive a considerable amount of damage. The tissues that have been irradiated exhibit varying degrees of inability to resist trauma and infection. Of all the tissues in the oral area, bone is the most likely to show degeneration when subjected to trauma or infection subsequent to radiotherapy. It is believed that all teeth that are going to be within the beam of radiation during radiotherapy should be extracted. Also, all infected or questionable teeth in the entire dentition should be removed prior to radiotherapy. Such extractions should be done at least ten days before radiotherapy is begun, so as to allow for healing of the damaged tissues. Dental extractions in an area that has had radiotherapy are extremely dangerous, since osteoradionecrosis could easily result from trauma or infection in these cases. A minimum of trauma and pre- and postoperative antibiotic therapy are desirable when such a tooth must be extracted. Such cases should be handled only by competent oral surgeons, and preferably in conjunction with a radiotherapist. When osteoradionecrosis does occur, the treatment is usually in the form of a sequestrectomy or a resection of the bone. The effect of x-radiation upon the developing dentition is seen only when large doses of x-radiation are used. Such doses, when administered to developing teeth, produce a variety of effects; the result is largely dependent upon the stage of formation of the individual teeth. Variations from normal can range from retarded or imperfect calcification to partial anodontia.

Physical factors that influence tissue dose, and thus tissue reaction, are of great importance in dentistry. Before proceeding with a discussion of these factors, it is desirable that some information about the units used in radiation dosimetry be given. The roentgen is the unit of measurement of x-rays; this measurement is made in air. It indicates the creation of ion pairs carrying or totaling one electrostatic unit of electricity in 1 c.c. of

standard air by the absorption of the x-ray photons.* For tissue doses, two units of measurement appear in the literature, the roentgen absorbed dose (RAD) and the roentgen equivalent physical (REP).† These two units are basically alike in that they represent energy or ion pairs in an amount relatively similar to that of a roentgen, but these now occur in one gram of tissue.‡

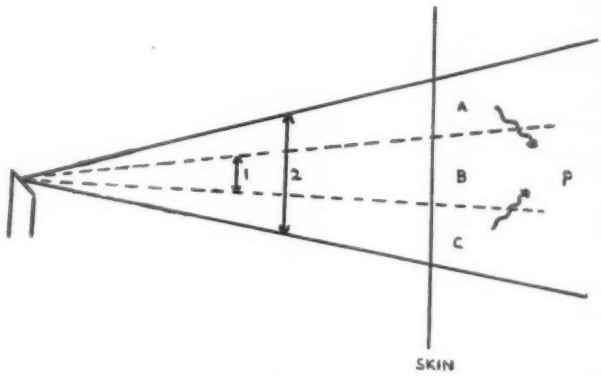


Fig. 6.—Diagram showing two beams of x-rays (*1* and *2*) of different size. The dose administered to the same point (*P*) within tissue by Beam 1 is less than that administered by Beam 2, due to the fact that scatter radiation originating in areas *A* and *C* reaches this point only when Beam 2 is used and not when Beam 1 is used.

It has been known for some time that the tissue reaction to a given dose of x-radiation is less when it is given in small fractionated doses than when it is given in one massive dose. Nevertheless, the small repeated doses of x-rays used in dentistry should be kept as small as possible. It is necessary, at this point, to stray away from the subject of biologic effects and discuss briefly certain aspects of technique related to dosage. The dose to any given point within a beam of radiation increases with the size of the beam of radiation. This is brought about by the fact that scatter radiation from other areas within the beam also reaches this point. This is shown diagrammatically in Fig. 6.

Collimating the beam of x-rays emanating from the dental machine with a lead diaphragm to the smallest practicable size is therefore desirable; moreover, the tissues outside the area under examination will be removed from the primary beam of radiation.

The x-ray dose administered to tissues during dental roentgenography can also be reduced by filtration. The x-ray beam consists of photons having

*_The roentgen:_ Standard unit of absorption of x-radiation and gamma radiation. The quantity of x-radiation or gamma radiation is such that the associated corpuscular emission per 0.0012938 gram of air (1 c.c. of dry air at standard temperature and pressure) produces, in air, ions carrying one electrostatic unit of a quantity of electricity of either sign.

†_The Roentgen Equivalent Physical (REP):_ That amount of ionizing radiation which, in tissue, produces the same amount of ionization as that produced by one roentgen in air. The dose of radiation (other than that covered by definition of the roentgen) which produces energy absorption of 93 ergs per gram of tissue.

‡_The Roentgen Absorbed Dose (RAD):_ The dose of radiation which produces energy absorption of 100 ergs per gram of tissue.

many different wave lengths. The x-rays of longer wave lengths, which are almost entirely absorbed by the tissues before they can reach the film, should be removed from the x-ray beam before they reach the patient. This is done by using an aluminum filter in the x-ray machine. The use of available fast films will also considerably reduce the patient's and the operator's dosage of x-radiation during intraoral roentgenography.

One physical factor which does not directly pertain to dentistry, but which greatly influences the tissue reaction, is the type of ionizing radiation used in damaging the tissue. X-rays, as well as particles without electrical charges, are very penetrating radiations. Generally speaking, these radiations are absorbed over great areas. Radiations carrying electrical charges, such as electrons and alpha particles, are affected by the electrostatic fields within atoms and tend to give up their energy through ionization in small areas. Therefore, radiations carrying the same amount of energy can result either in heavy ionization of a small amount of tissue or in light ionization of a large amount of tissue, depending upon the type of radiation used.

WHOLE-BODY EFFECT OF X-RADIATION

Whole-body irradiation is measured in REPs; the whole-body dose indicates the amount of radiation that is received by each gram of tissue in the entire organism. This fact must be remembered whenever one speaks of the dose received by a given amount of tissue; this specific area dose must be differentiated from the dose received by the whole body. There is likely to be confusion concerning this point, since therapeutic doses of x-radiation given to limited amounts of tissue are quite often more than 2,000 REPs, whereas 600 REPs of whole-body radiation administered to a human being results more often than not in the death of the patient. There is little information on the effects of large doses of whole-body irradiation in human beings, but studies made of the atomic bomb victims in Japan as well as animal experiments throw some light upon this subject.

Whole-body irradiation can be divided into two types, acute and chronic. It is almost impossible to obtain the acute type with a dental machine, for the output of such a machine is too low. This type of irradiation would probably be experienced only by atomic bomb victims or through accidental exposure to high-energy sources of radiation. It is difficult to say how much whole-body radiation must be given to produce a certain effect; this varies from one species of animal to another and even between animals of the same species. A discussion of the so-called "radiation syndrome" is therefore omitted from this article.

The chronic type of whole-body irradiation is of more interest to the dentist. This occurs from the scattered radiation, and most of this radiation originates from the patient. It must be noted that the penetrating ability of the x-rays used in dentistry is not great enough to produce an even dose to all the tissues of the body. The dose measured at the skin of the x-ray operator is

accepted as the whole-body dose of radiation. The safety factor, resulting from the fact that the deeper tissues receive a much lower dose than the skin, is desirable; this is especially true since the biologic effects of ionizing radiations are not fully understood. All dentists should note that prior to 1957 the recommended maximum dose of whole-body radiation for persons working with x-radiation was set by the National Bureau of Standards at approximately three-tenths (0.3 r) of one roentgen per week. In 1957 this recommended maximum dose was lowered by two-thirds to approximately one-tenth (0.1 r) of one roentgen per week.

There is much concern among geneticists about the long-term cumulative effects of small doses of x-radiation. This is due not only to the genetic problem but also to the fact that available information indicates that these small doses may be a causative factor in an increase in the number of cases of leukemia in the United States. It has also been suggested that the reduced life span of medical radiologists may be the result of the cumulative effect of small doses of x-rays. Estimations of the dose necessary to shorten a person's life by one day vary from 1 to 15 REPs.

GENETIC EFFECTS OF X-RADIATION

The effects of x-radiation upon the reproductive cells are similar to those occurring in other cells; this includes the breaking of chromosomes and the production of point mutations. The point mutation is the most elusive and the most important of all the different genetic changes. Studies have been made of these genetic changes in many different forms of life, such as viruses, bacteria, plants, and animals. Man has also been studied to some extent by examinations made on the descendants of exposed persons and by observation of the results of inbreeding among human beings. From all the accumulated data, geneticists draw certain broad conclusions. Observations made by geneticists point to the existence in animals of a spontaneous rate of point mutation. The rate of point mutation can be increased by irradiating the genetic material of animals. Whether they be of a spontaneous or induced type, the overwhelming majority of mutations are of a detrimental nature. It is believed that evolution takes place through the multiplication of the rare advantageous point mutation.

Many persons envision the result of a deleterious point mutation to be a freak or monstrosity. Such is not the case, however; such a result is extremely rare. The new organism receives a complete set of genes from each parent. If a mutant gene is present in the set from one parent, its action is similar to that of a recessive gene, and the comparable gene in the set received from the other parent plays the dominant role. The result is that there is so little impairment to the new organism that large colonies of irradiated organisms have to be studied before statistical evidence will indicate some impairment of the ability of these organisms to live and reproduce. It must be remembered that the mutant gene will be transmitted from generation to generation and that its effect will be felt not only by one person but by many.

Whenever an organism receives a mutant gene of the same type from both parents, there exists the possibility of the organism's death, but the cases in which this result is seen are definitely in the minority. The majority of organisms receiving similar mutant genes from both parents will show some impairment, but few of this group will show any visible signs of disfigurement. It is therefore thought that x-radiation can be given to a small section of the population without producing any visible damage in succeeding generations. Genetic effects become a menace, however, when large sections of the population receive x-radiation or any other form of ionizing radiation.

PUBLIC HEALTH ASPECTS OF X-RADIATION

"Radiologic health" is the term used when the effects of x-radiation on groups of persons or on populations are considered. With the beginning of the atomic age, the biologic effects resulting from exposure of the public to ionizing radiations became important, and an understanding of the hazards of ionizing radiations became essential. Previous to the first atomic explosion, most of the man-made x-radiation was controlled in laboratories, institutions, and medical and dental offices. Today ionizing radiations are being used extensively in industry, and radioactive fallout from atomic bomb tests reaches all parts of the globe. Increasing amounts of ionizing radiations are now being absorbed by whole populations of human beings. The effect of this increase cannot, of course, be shown at this time. Experiments done with insects and animals provide much information about this most vital phenomenon.

It must be remembered that man has always lived with gamma radiation, which has physical properties identical with man-made x-radiation. These gamma radiations reach us from radioactive minerals in building materials, rocks, and ground. Man is also affected by cosmic radiations that penetrate the atmosphere and reach the surface of the earth. Collectively these radiations are called background radiations; their most important effect is that of increasing the spontaneous mutation rate in man.

Present-day information indicates that there is a linear relationship between raising the gonadal radiation dose and the frequency of induced point mutations. The only conclusion that can be drawn from this information is that there is no safe dose of x-radiation for genetic tissue. The problem today, however, is not how to eliminate the sources of x-radiation but how to live with them. Deleterious mutations are eliminated from populations at a certain rate through the "genetic death" of the persons carrying these mutant genes. The term "genetic death" implies that the individual is either incapable of reproducing or dies before reproduction can take place. It is felt that there is a certain mutant burden that man can absorb without future generations having an increase in conspicuous abnormalities or a shortening of the life span. The United Nations, the National and International Committees on Radiation Protection, the Medical Research Council of Great Britain, and the National Academy of Sciences of the United States of America recommend that the "permissible dose" of man-made ionizing radiations for the gonads be no more

than a total of 10 roentgens to any person when delivered between the time of conception and the age of 30. For persons using ionizing radiations in their occupations, however, the recommendation is that the "permissible dose" be raised to no more than 50 roentgens for every ten working years. Dentists should keep in mind that these dose levels may have to be lowered in the future if new information gained in this field indicates a necessity to do so. The age of 30 is used as a guide in the United States, since most American children are born when their parents are less than 30 years of age. This does not mean that when the patient is over 30 years of age there is no danger in irradiating the gonads. It is the responsibility of any dentist who possesses an x-ray machine to see that all necessary precautions are taken to keep the exposure of patients and operators to the lowest possible dose consistent with good diagnostic oral roentgenography.

The biologic effects of x-radiation are of such a complex nature that one is unable to grasp fully the limited present-day knowledge of this subject. The fact remains that x-radiation delivered to persons in the dental office can have undesirable effects. It must be kept in mind that if x-rays are properly used, roentgenograms can be made with such small doses of x-radiation that the patient and the operator receive very little radiation. The dentist need not fear that he is injuring his patient or himself; the wealth of information obtained from diagnostic roentgenograms far outweighs the possibility of any injurious biologic change. However, good roentgenographic technique and an understanding of x-radiation are two prerequisites for the conscientious operator. The expression "You can't see the forest for the trees" can well be applied to this subject. It is hoped that the presentation of this material in a simplified manner has given the reader a glimpse of this forest of biologic effects.

REFERENCES

1. Glasser, O., Quimby, E. H., Taylor, L. S., and Weatherwax, J. L.: Physical Foundations of Radiology, ed. 2, New York, 1952, Paul B. Hoeber, Inc.
2. Young, H. H., and Kunkel, M. G.: Diagnosis, Treatment and Prognosis of Roentgen Ray Injuries to Dentists, J. Am. Dent. A. 51: 1-7, 1955.
3. Haagensen, C. D.: Occupational Neoplastic Disease, Am. J. Cancer 15: 641-703, 1931.
4. Carroll, R. E., Godwin, J. T., and Watson, W. L.: Osteogenic Sarcoma of Phalanx After Chronic Roentgen-Ray Irradiation, Cancer 9: 753-755, 1956.
5. The Responsibilities of the Medical Profession in the Use of X-rays and Other Ionizing Radiations, Statement by the United Nations Scientific Committee on the Effects of Atomic Radiation, 1957.
6. Hearings Before the Subcommittee on Research and Development of the Joint Committee on Atomic Energy, Congress of the United States, June 4-8, 1956; May 27-29 and June 3, 1957; June 4-7, 1957, Washington, U. S. Government Printing Office.
7. Wolstenholme, G. E. W., and O'Connor, C. M. (editors): Ciba Foundation Symposium: Ionizing Radiations and Cell Metabolism, Boston, 1956, Little, Brown & Company.
8. The Basic Aspects of Radiation Effects on Living Systems, Symposium on Radiobiology, New York, 1952, John Wiley & Sons, Inc.
9. Bloom, W.: Histopathology of Irradiation, New York, 1948, McGraw-Hill Book Company, Inc.
10. Ellinger, F.: Medical Radiation Biology, Springfield, Ill., 1957, Charles C Thomas Publisher.
11. Lawrence, J. H., and Hamilton, J. G.: Advances in Biological and Medical Physics, New York, 1951, Academic Press, Inc., Vol. II.

12. Lea, D. E.: Actions of Radiations on Living Cells, ed. 2, London, 1955, Cambridge University Press.
13. Puck, T. T., and Marcus, P. I.: Action of X-rays on Mammalian Cells, J. Exper. Med. **103:** 653-666, 1956.
14. Bender, M. A.: X-ray Induced Chromosome Aberrations in Normal Diploid Human Tissue-Cultures, Science **126:** 974-975, 1957.
15. MacComb, W. S., and Quimby, E. H.: The Rate of Recovery of Human Skin From the Effects of Hard or Soft Roentgen Rays or Gamma Rays, Radiology **27:** 196-207, 1936; **29:** 305-312, 1937.
16. Spear, F. G.: On Some Biological Effects of Radiation, Brit. J. Radiol. **31:** 114-123, 1958.
17. Merriam, G. R., and Focht, E. F.: A Clinical Study of Radiation Cataracts and Relationship to Dose, Am. J. Roentgenol. **77:** 759-783, 1957.
18. Billings, M. S., Norman, A., and Greenfield, M. A.: Gonad Dose During Routine Roentgenography, Radiology **69:** 37-41, 1957.
19. Baily, N. A.: Patient Exposure to Ionizing Radiation in Dental Radiography, Radiology **69:** 42-45, 1957.
20. Dobzhansky, T.: Evolution at Work, Science **127:** 1091-1098, 1958.
21. Dobzhansky, T.: Genetic Loads of Natural Populations, Science **126:** 191-194, 1957.
22. Meyer, I.: Osteoradionecrosis of the Jaws, Practical Dental Monograms, November, 1958.
23. Plough, H. H.: Radiation Tolerances and Genetic Effects, Nucleonics **10:** 16-20, 1952.
24. Martin, J. H.: Radiation Doses to the Gonads in Diagnostic Radiology and Their Relation to the Long-Term Genetic Hazard, M. J. Australia **2:** 806-810, 1955.
25. Stanford, R. W., and Vance, J.: The Quantity of Radiation Received by the Reproductive Organs of Patients During Routine Diagnostic X-ray Examination, Brit. J. Radiol. **28:** 266-273, 1955.
26. Lamerton, L. F.: An Examination of Clinical and Experimental Data Relating to the Possible Hazard to the Individual of Small Doses of Radiation, Brit. J. Radiol. **33:** 229-239, 1958.
27. Noel, J. V.: The Delayed Effects of Ionizing Radiations, J. A. M. A. **166:** 908-915, 1958.
28. Lewis, E. B.: Leukemia and Ionizing Radiation, Science **125:** 965-972, 1957.
29. Dunlap, C. E.: Delayed Effects of Ionizing Radiation, Radiology **69:** 12-17, 1957.
30. Stone, R. S.: The Concept of a Maximum Permissible Exposure, Radiology **58:** 639-661, 1952.
31. Failla, G.: Considerations Bearing on Permissible Accumulated Radiation Doses for Occupational Exposure, Radiology **69:** 18-22, 1957.
32. Macht, S. H., and Lawrence, P. S.: National Survey of Congenital Malformations Resulting From Exposure to Roentgen Radiation, Am. J. Roentgenol. **73:** 442-466, 1955.
33. Henshaw, P. S.: Genetic Transition as a Determinant of Physiologic and Radiologic Aging and Other Conditions, Radiology **69:** 30-36, 1957.
34. Muller, H. J.: Radiation Damage to the Genetic Material; Science in Progress, Seventh Series, New Haven, 1951, Yale University Press, pp. 93-165.
35. Ingraham, S. C., Terrill, J. G., Jr., and Moeller, D. W.: Concepts of Radiological Health, U. S. Public Health Service Publication No. 336, January, 1954.
36. National Academy of Sciences: The Biological Effects of Atomic Radiation; Summary Report, Washington, D. C., 1956.
37. Medical Research Council (Great Britain): The Hazards to Man of Nuclear and Allied Radiations, London, 1956, Her Majesty's Stationery Office.
38. Behrens, C. F.: Permissible Dosage and Risk Factors, In Atomic Medicine, ed. 3, Baltimore, 1959, Williams & Wilkins Company, pp. 278-310.
39. National Bureau of Standards: Maximum Permissible Radiation Exposures to Man, Handbook No. 59, Washington, D. C., 1957.
40. Muller, H. J.: Potential Hazards of Radiation, Exerpta Med. (Amsterdam) **2:** 223-225, 1957.

A MICROROENTGENOGRAPHIC INVESTIGATION OF DEMINERALIZED ENAMEL, COMPARING NATURAL AND ARTIFICIAL LESIONS*

*Ernest Newbrun, B.D.S., M.S.,** Finn Brudevold, D.D.S., M.S.,*** and Herbert Mermagen, B.S., Rochester, N. Y.*

INCIPIENT enamel caries is usually first seen as a whitish area characterized by decalcification of enamel under an apparently intact surface. The microstructural changes involved have been described by many workers using transmitted or polarized light microscopy or roentgenographic procedures. Recent work has shown that the lesion can be reproduced in vitro by incubating teeth in bread-saliva mixtures[1] or in lactose broth inoculated with various strains of acidogenic bacteria.[2] It can also be reproduced by exposing teeth to 0.075 per cent lactic acid,[2, 3] 0.5 M lactate ranging in pH from 4.1 to 5.3,[4] or calcium phosphate buffers in the pH range of 4.0 to 5.0.[5] From these studies, it can be concluded that the first stages of the carious process are characterized by decalcification rather than by proteolysis[3] and that decalcification is selective in that subsurface enamel is dissolved at a greater rate than the outer surface. The protection of the surface enamel has been ascribed to the presence of the enamel cuticle,[2] to hypercalcification of the outer enamel,[4] and to the presence of high concentrations of fluoride and other trace elements which are known to accumulate in the outer enamel.[6, 7] It has been postulated that acid penetrates the outer enamel through defects,[3] through the interprismatic substance,[4] or through pores developed by preferential dissolution of the more soluble constituents of enamel, such as carbonate.[6] Most investigators agree that the lesion advances in subsurface enamel in two directions: along the prisms and along the striae of Retzius. The advance along the prisms has been attributed to greater solubility of interprismatic than prismatic substance[6] and to the relatively high permeability of the prism sheath.[8] The decalcification along the striae of Retzius has been considered due to rhythmic variation in extent of mineralization[3] and to the presence of permeable organic material.[8]

From the Eastman Dental Dispensary and the University of Rochester Atomic Energy Project.

This work was supported by United States Public Health Service Grant No. D-391.

*Based on a thesis submitted by the senior author in partial fulfillment of the requirements for the Master of Science degree, University of Rochester, 1957.

**Present address: University of Alabama, School of Dentistry, Birmingham, Alabama.

***Present address: Forsyth Dental Infirmary and Harvard School of Dental Medicine, Boston, Massachusetts.

From the foregoing, it is evident that the selective decalcification in carious lesions is not well understood. The present work is part of a study designed to investigate the nature of the acid resistance of surface enamel as compared to subsurface enamel. Teeth were exposed to high concentrations of lactate buffers of different pH or incubated in saliva-sugar mixtures, and the lesions thus produced were compared with incipient enamel caries by means of a microroentgenographic procedure.

MATERIALS AND METHODS

Freshly extracted sound teeth and teeth with initial caries were selected for study. After being cleaned, the sound teeth were coated with blue inlay wax and a small window was exposed on the buccal, lingual, or proximal surface of the crown. The teeth thus prepared were exposed for varying periods of time to 10 ml. of 1 M lactate buffers ranging in pH from 3.7 to 5.1. The pH did not change during the test. Teeth were also incubated at 37° C. in a mixture of 9 ml. of paraffin-stimulated saliva and 1 ml. of a 20 per cent glucose solution for different periods of time. Planoparallel ground sections of the lesions, 60 to 120 microns thick, were prepared according to a modification of the technique described by Hammarlund-Essler.[9] Microroentgenograms were obtained on Kodak spectrographic plates No. 649-0 which have a fine-grained emulsion capable of reproducing 1,000 lines per millimeter. Roentgen-ray exposures were made of the section at a target distance of 11 cm. with a low-voltage machine equipped with a General Electric defraction tube with a copper target. The machine was operated at 20 KVP and a 10 milliampere tube current. The emerging radiation was predominantly the Kα characteristic radiation for copper with a wave length of 1.54 angstroms.

A few microdensitometric tracings were obtained of roentgenograms of carious lesions and adjacent sound enamel using a microdensitometer designed by the Eastman Kodak Company.[10] This machine had a high resolving power and was sensitive to very low levels of light. The microroentgenogram was moved mechanically across a fine beam of light, and the logarithm of the ratio of the intensity of light striking the film to the intensity of light passing through the film was plotted by an automatic recorder.

RESULTS

Microroentgenograms of surface carious lesions are shown in Fig. 1, *A* and *B*. The roentgenopaque surface layer can be seen clearly against the decalcified subsurface enamel. Fig. 1, *A* shows the preferential dissolution of mineral salts between the striae of Retzius. There can be seen roentgenolucent lines which suggest demineralization of the interprismatic substance, while the enamel prisms remain fairly well calcified. This is shown at a greater magnification in Fig. 1, *B*.

The results of acid etchings of thirty-nine sound teeth are summarized in Fig. 2. Here changes at the experimental enamel surface are assigned to one

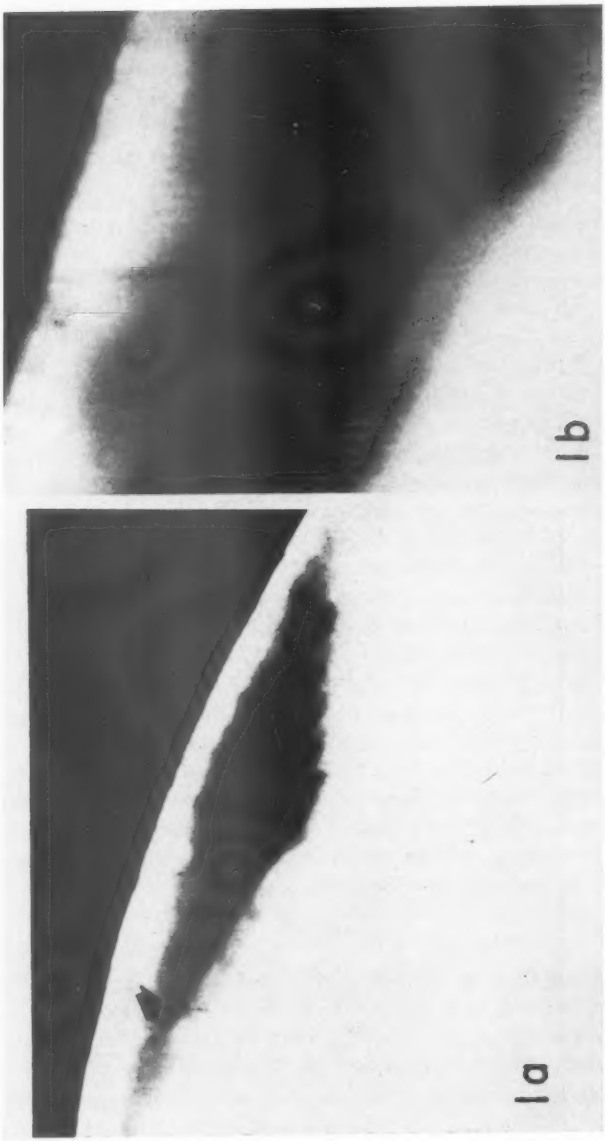


Fig. 1.—Microroentgenograms of an initial carious enamel lesion. The arrow in *A* indicates the stria of Retzius remaining after the surrounding enamel has been dissolved. At higher magnification (*B*), note demineralization of interprismatic substance. (Original magnifications, ×100 and ×430; reduced ⅓.)

of three categories, namely: (1) subsurface decalcification where a roentgenolucent area was found covered by a roentgenopaque surface layer, (2) cavitation involving a distinct loss of substance from the surface and presenting a hollowed-out appearance, (3) serration giving a stepped or saw-blade appearance to the surface. Frequently serration occurred simultaneously with cavitation, so that the floor of the induced cavity was of a stepped character.

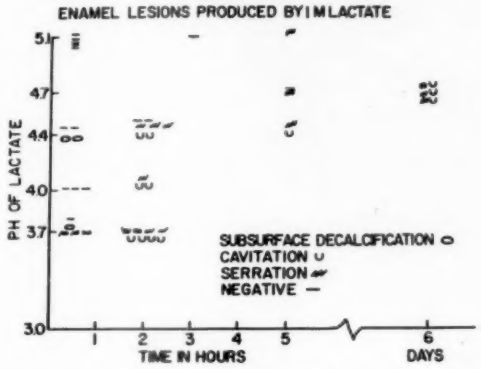


Fig. 2.—Summary of enamel lesions produced by 1 M lactate.

Subsurface lesions were found in only three teeth which were exposed for twenty minutes, one at pH 3.7 and two at pH 4.4 Three other teeth exposed for twenty minutes at pH 3.7 showed serration and one showed no effect. The remaining ten teeth which were exposed for twenty minutes at pH 4.0 to 5.1 had no visible decalcification. Etching for two hours produced cavitation

Fig. 3.—Microroentgenogram of enamel following treatment by 1 M lactate buffer at pH 3.7 for two hours. Preferential dissolution of interprismatic material may be seen. (Original magnification, ×430; reduced ⅓.)

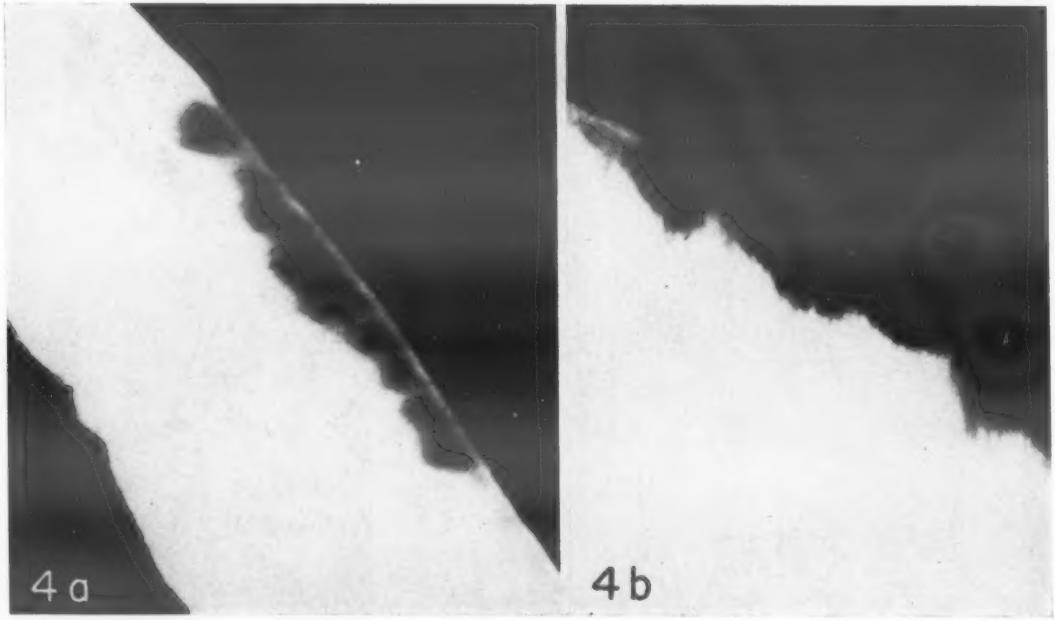


Fig. 4.—*A*, Microroentgenogram of enamel following saliva-glucose incubation for nine days. Observe the subsurface decalcification. (Original magnification, ×100; reduced ⅛.)
B, Microroentgenogram of enamel following saliva-glucose incubation for ten days. Both cavitation and subsurface demineralization have occurred. (Original magnification, ×180; reduced ⅛.)

and/or serration in all instances at pH 4.0 or below and in most instances at pH 4.4. More prolonged acid exposure was required to produce lesions at pH 4.7 and pH 5.1. The preferential dissolution of interprismatic substance in acid-exposed enamel is shown in Fig. 3. Note the resemblance to the microroentgenogram of the carious lesion in Fig. 1, *B*.

The results of incubation of teeth in the saliva-glucose medium are summarized in Table I. As an initial test, one tooth was incubated for two days, another for four days, and so on up to ten days. More striking results were obtained after eight days of incubation, and subsequent tests were carried out over longer time intervals (8 to 13 days). After incubation for eight days or longer (final pH 4.5), all teeth showed some chalkiness and a change in translucency of the exposed surface. Microroentgenographically, most teeth thus treated showed pronounced subsurface demineralization with a distinct roentgenopaque surface layer, which in a few instances was interrupted. In general, the roentgenolucent area produced did not extend far into the enamel, as compared to the natural lesions examined. The inner edge of the demineralized zone usually presented a serrated border. A microroentgenogram of a typical lesion, obtained after nine days' incubation, is shown in Fig. 4, *A*. The subsurface roentgenolucency is continuous and covered by a thin layer of roentgenopaque enamel. Fig. 4, *B* shows a microroentgenogram of a lesion after ten days' incubation. Both cavitation and subsurface demineralization have occurred. The serrated interior border of the lesion is similar to that seen in caries (Fig. 1, *A*) and is related to the striae of Retzius. There is a suggestion of preferential loss of interprismatic material, as was the case in carious and acid-etched lesions.

TABLE I. ENAMEL LESIONS PRODUCED BY INCUBATION IN SALIVA-GLUCOSE AT 37° C., FINAL pH 4.5

NUMBER OF TEETH	TIME (DAYS)	NO CHANGE	TYPE OF LESION		
			CAVITATION	SERRATION	SUBSURFACE
1	2	1			
1	4				1
1	7	1			
11	8-13		3	1	8

Microdensity tracings of x-ray plates from the surface to the dentinoenamel junction of sound enamel and an initial carious lesion are shown in Fig. 5. Here the photographic density of the plate is plotted on the ordinate, and the distance from the enamel surface is plotted on the abscissa. The photographic density of an expoosed x-ray plate is the common logarithm of the ratio of the amount of light striking one side of the plate compared to the amount of light that passes through the plate.

$$D = \log \frac{I_o}{I_t}$$ where D = photographic density,

I_o = intensity of incident light,

I_t = intensity of transmitted light.

There is an inverse relationship between the photographic density of the roentgenogram and roentgenopacity of the specimen or, in the case of enamel, the degree of calcification.

The recording of sound enamel exhibits a peak in roentgenopacity (lowest photodensity) at the outer edge and a decrease toward the dentinoenamel junction (highest photodensity). Hodge and associates[11] and Thewlis[12] have observed a similar peak and steady decrease in roentgenopacity of sound enamel. Thewlis has shown that the peak was not merely due to a photographic effect, known as the Mackie effect, but could be attributed to true changes in x-ray absorption. The photodensity tracing of the roentgenogram of an incipient carious lesion (Fig. 5) shows a low value at the outer surface (high roentgenopacity); a pronounced increase in photodensity (low roentgenopacity) just inside the enamel surface demonstrates marked decalcification. Contrary to the findings in sound enamel, the photodensity of the surface enamel over the carious lesion is greater than that of subsurface sound enamel (roentgenopacity is less). This indicates that partial decalcification of the apparently intact surface has taken place.

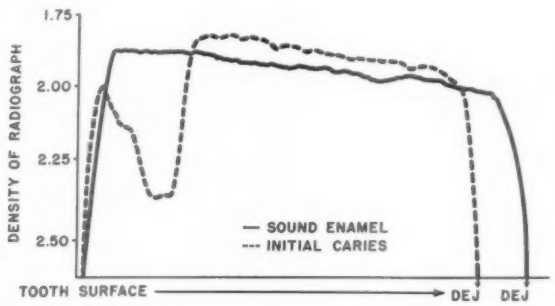


Fig. 5.—Photodensity tracings of microroentgenograms of sound enamel and initial enamel caries.

DISCUSSION

The present work substantiates the findings of others that carieslike subsurface lesions can be produced in vitro. These lesions were obtained consistently after incubation in saliva-glucose mixtures but rarely in the lactate buffers, and then only after short exposures. The most obvious cause for the different decalcification patterns produced by the two solutions is the difference in concentration of the acids. Titrations showed the acidity of the incubated saliva-glucose mixture to be approximately 0.01 M, as compared to 1.0 M for the lactate buffer. Koulourides[13] has reported that increasing the buffer concentration while maintaining a constant pH will increase the rate of dissolution of powered enamel. Therefore, the more rapid decalcification produced by the lactate, as contrasted with that produced by the saliva-glucose mixture, would be expected. The virtual absence of subsurface lesions in the teeth exposed to the lactate suggests that the resistance of the surface enamel is overcome by strong decalcifying agents. As a result, a breakdown of the outer

enamel in the form of serration or cavitation occurs before the acid reaches the subsurface enamel. According to this concept, weak buffers should be more likely to produce subsurface lesions than strong buffers. Hals and associates[4] did in fact obtain a relatively great number of subsurface lesions when they used a lactate buffer of one-half the concentration employed in the present study.

The presence of phosphate in saliva is another factor which may favor development of subsurface lesions. The observation of Coolidge and Besic[5] that phosphate buffers in the pH range of 4.0 to 5.0 produced carieslike lesions supports this view. Studies in this laboratory have shown that the presence of phosphate in decalcifying solutions will cause dissolution of relatively large amounts of carbonate from powered enamel, while the loss of calcium phosphate is retarded. The phosphate in the incubated saliva-glucose mixture may, therefore, promote preferential dissolution of carbonate from the surface enamel and thus create porosity which may permit penetration of acid into the bulk of the enamel. The presence of cracks or hypoplastic defects in the surface enamel is evidently not needed for acid penetration. The photodensity tracings of roentgenograms of carious lesions consistently showed partial decalcification of the outer surface, and microscopic examination of numerous sections and microroentgenograms revealed no visible break in the surface continuity. Once acid has gained access to inner enamel, relatively rapid decalcification may be expected, for it has been shown conclusively that subsurface enamel dissolves more readily in acid than does surface enamel.[7]

The majority of lesions produced by the 1 M lactate buffer showed remarkable roentgenographic similarity to advanced enamel caries when cavitation had already taken place. For example, the apparent loss of interprismatic structure with bristlelike remnants of prisms, as shown in the microroentgenograms of the acid-etched area in Fig. 3 and the carious lesion in Fig. 4, *B*, was frequently observed. Another similarity was the relationship of serrated margins of both types of lesions to the striae of Retzius.

Studies have shown marked differences between the composition of surface or subsurface enamel, which undoubtedly is related to the difference in solubility. For example, the high fluoride[14] and low carbonate concentration[15] in outer enamel, as compared to inner enamel, should materially increase the acid resistance of the former. A recent study has shown that the different solubility of surface and subsurface enamel persists after the organic constituents have been removed.[7] Projecting this observation to the microstructures of the enamel, it may be postulated that the selective decalcification seen in carious enamel is associated with chemical or physical differences in the inorganic phase of various structures.

SUMMARY

1. The microroentgenographic appearance of initial carious lesions occurring as white spots has been described.

2. Artificially produced lesions were also investigated by a microroentgenographic technique and confirmed several of the findings on natural lesions.

3. Saliva-glucose incubation for periods of eight to thirteen days at 37° C. confirmed the resistance of the surface layer and the greater solubility of the subsurface enamel.

4. Acid-etched areas produced by exposure of sound enamel to 1 M lactate buffer at a pH of 3.7 to 5.1 simulated a later stage of natural demineralization. The palisade structure observed implied an inward invasion of acid affecting the interprismatic material more than the prisms. The "stepped" character of the floor of these areas emphasized the different solubility of the incremental layer.

REFERENCES

1. Keil, A.: Über die Initialstadien der Schmelz-Karies und ihre Erzeugung in Kaubrei-Versuchen in vitro, Deutsche Zahn. Ztschr. 4: 947, 1949.
2. Darling, A. I.: The Distribution of the Enamel Cuticle and Its Significance, Proc. Roy. Soc. Med. 36: 499, 1943.
3. Darling, A. I.: Studies of the Early Lesions of Enamel Caries With Transmitted Light, Polarized Light and Radiography, Brit. D. J. 101: 289, 329, 1956.
4. Hals, E., Morch, T., and Sand, H.: Effect of Lactate Buffers on Dental Enamel In Vitro as Observed in Polarizing Microscope, Acta odont. scandinav. 13: 85, 1955.
5. Coolidge, T. B., and Besic, F. C.: A Microscopic Comparison of Clinically and Artificially Produced Changes in Enamel, ORAL SURG., ORAL MED. & ORAL PATH. 8: 1204, 1955.
6. Guzman, C., Brudevold, F., and Mermagen, H.: A Soft Roentgen-ray Study of Early Carious Lesions, J. Am. Dent. A. 55: 509, 1957.
7. Isaac, S., Brudevold, F., Smith, F. A., and Gardner, D. E.: Solubility Rate and Natural Fluoride Content of Surface and Subsurface Enamel, J. D. Res. 37: 254, 1958.
8. Sullivan, H. R.: The Formation of Early Carious Lesions in Dental Enamel, J. D. Res. 33: 231, 1954.
9. Hammarlund-Essler, E.: A Method of Preparing Ground Sections for Microradiography and Autoradiography, Acta odont. scandinav. 13: 167, 1955.
10. Altman, J. H., and Stultz, K. F.: Microdensitometer for Photographic Research, Rev. Scientific Instr. 27: 1033, 1956.
11. Hodge, H. C., VanHuysen, C. F., and Warren, S. L.: Factors Influencing the Quantitative Measurement of the Roentgen Ray Absorption of Tooth Slabs, Am. J. Roentgenol. 37: 529, 1937.
12. Thewlis, J.: Calcification of Enamel and Dentin, Brit. D. J. 62: 303, 1937.
13. Koulourides, T. J.: The Effect of Organic Anions on Enamel and Dentin Solubility Rate in Acid Buffers, M. S. Thesis, University of Rochester, 1958.
14. Brudevold, F., Gardner, D. E., and Smith, F. A.: The Distribution of Fluoride in Human Enamel, J. D. Res. 35: 420, 1956.
15. Little, M. F., and Brudevold, F.: Distribution of Inorganic Carbonate in Human Enamel, J. D. Res. (Abst.) 34: 708, 1955.

ORAL PATHOLOGY

HEMIATROPHY OF THE FACE

Report of a Case

J. S. Knight, Ph.D., B.D.S., H.D.D., and
J. R. Moore, F.D.S.R.C.S., B.D.S., Worcestershire, England

THE patient, a 39-year-old woman, complained of a progressive shrinking of the left side of her face. Since childhood she had noticed a small area of discolored white skin over the lower border of the mandible in the left premolar region. This remained unchanged until 1945, when a localized swelling occurred in relation to this white area. The swelling came up rapidly as "a great red lump"; it was tender to touch and was diagnosed as a dental abscess. Treated with poultices, it went down after ten days, leaving a tiny fibrous nodule which very slowly increased in size for some two years. At the same time the patient noticed that her face on that side was shrinking slowly. This last symptom was accompanied by trismus, since the facial muscles on the affected side went into spasm for short periods. These attacks of spasm gradually passed away, but the atrophy continued until she appeared as shown in the photographs taken in 1955 (Figs. 1 to 4).

Examination.—The left side of the face was puckered and drawn, with marked shrinkage over the left mala, maxilla, and mandible (Fig. 1). The small scar or fibrous nodule mentioned above was seen at the lower border (Figs. 2 and 3). There was marked enophthalmos of the left eye. The left cheek and the floor of the mouth felt thin and lacking in body, apparently due to wasting of fat and connective tissue, for the muscles could be palpated when the teeth were clenched. The patient was edentulous; the last teeth had been extracted two years previously, but there was excessive shrinkage of the edentulous alveolar processes and of the maxilla and antral walls on the left side as compared with the right. The tongue appeared normal.

A detailed medical history revealed nothing of importance, except bronchitis in the wintertime over a long period and the onset of diplopia some two years earlier, presumably as a result of the enophthalmos. The latter symptom had been treated with glasses.

Special tests and investigations included the estimation of serum calcium, phosphorus, and alkaline phosphatase, a complete blood investigation, and roentgenograms of the chest, pelvis, and long bones. These investigations revealed no abnormality. Roentgenograms of the jaws, however, showed that there was osteoporosis of the bone of the left maxillary alveolus and antral wall (Fig. 4).

On the basis of the appearance, the history, and the examination, a diagnosis of hemiatrophy of the face was made.

From Birmingham Regional Plastic and Jaw Injury Unit, Wordsley Hospital, Nr. Stourbridge, Worcestershire, England.

Fig. 1.—Unilateral atrophy of face, front view.

Fig. 2.—Unilateral atrophy of face, left side showing atrophy.

Fig. 3.—Unilateral atrophy of face, left side showing result of smile on atrophied side.

Fig. 4.—Unilateral atrophy of face. Occipitomental roentgenogram showing osteoporosity in the left malar and maxillary regions.

DISCUSSION

Hemiatrophy of the face is an atrophic disorder of uncertain etiology characterized by progressive wasting of some or all of the tissues of one side of the face and sometimes extending beyond these limits. The disorder may involve skin, subcutaneous connective tissues, fat, cartilage, and bone.[1] The condition was first described in 1846 by Romberg; between that time and 1948, 410 cases were reported.[2]

The condition is sometimes congenital. It is usually a disorder of earlier life, however; it occurs most commonly in the second decade and becomes increasingly rare after this time. Males and females appear to be equally affected. Occasionally the disorder starts in the early years of life, following birth injury. As described in our case, the disease is often heralded by a small patch of discoloration at the point where atrophy begins. Wasting may begin anywhere on the face, and there is no predilection for the right or the left side. In some cases the atrophy remains limited to one region; in others it spreads slowly or quickly to involve half the face or even extends to the side of the neck or to the breast on the same side. Many cases terminate in a short period (six months to two years). Our case has continued for some eight years.

SYMPTOMS

When well marked, the face presents a striking appearance. The normal and abnormal halves are sharply divided sagittally by the coup de sabre. The abnormal side resembles the face of old age and the tongue, mucous membranes of the gingivae, and the soft palate may all be involved, although there is no muscular weakness. Pigmentation of the atrophic area, loss of hair of the face, eyebrows, or scalp, neuralgic pain associated with occasional tender spots, or more rarely facial anesthesia have been reported. Not infrequently there is a cervical sympathetic paralysis. Double vision, when present, is due to absorption of fat from the eye socket.

PATHOLOGIC ANATOMY

In the literature we have been able to discover only three cases in which a postmortem study of the pathologic changes has been carried out.[3] From these cases, the following observations were made:

1. The atrophy of the muscles in these cases was due to loss not of muscle fibers but of connective tissue and fat. The muscle fibers were preserved, and contraction could and did take place normally.
2. The facial cartilages affected were, in order of frequency, the nasal, the auricular, the laryngeal, and the tarsal, but only the nasal cartilages were commonly involved.
3. It is emphasized that bone involvement is directly proportional to the age period at which the hemiatrophy had its onset, which is

not surprising since it is considered that the disease affects young persons often before full development of the bony framework has taken place.

4. All showed a proliferative interstitial neuritis involving all branches of the trigeminal nerve from its Gasserian origin on the side affected.
5. All three patients had advanced tuberculosis.

PATHOGENESIS

Various theories have been advanced to explain the etiology of the condition, but none has yet accounted for all the facts. These theories are summarized as follows:

1. No significance can be ascribed to hereditary or endocrine factors or to the history of local trauma which may often be elicited.
2. Local infection is often mentioned, as in the case reported here. Thus, the disease is described as following extraction of teeth, alveolar abscess, adenitis, or local infected hematoma.
3. General infection:
   (a) Pulmonary tuberculosis, especially apical pleurisy of tubercular origin, is found associated with this condition almost too frequently to be coincidental.
   (b) The disease, though resembling scleroderma, is a separate entity. It has been linked with scleroderma by Cassirer, but in hemiatrophy the skin is not cicatricial but smooth and free. Furthermore, it is unilateral, whereas scleroderma is not.
4. The trigeminal theory arose because of the interstitial neuritis found in the necropsies, but it must be remembered that trigeminal neuritis is common whereas hemiatrophy is rare.
5. The sympathetic theory suggests that atrophy occurs due to a disturbance of function of the trophic fibers. Muller[4] suggested that the sympathetic nervous system was concerned with trophicism and that the trophic fibers course partly with the peripheral sensory nerve fibers and partly with the fibers accompanying the vascular apparatus, there being separate trophic and vasomotor fibers. It has been possible, therefore, to show that the sympathetic disturbance may be followed either by vasomotor or trophic changes or both. This theory is supported by the several cases in which hemiatrophy resulted from lesions compressing or otherwise injuring the cord and cervical sympathetic nerves; furthermore, the presence of a concomitant Horner's syndrome has been demonstrated in many lesions, especially those occurring in such conditions as syringomyelia or brachial plexus injuries. Several cases of accidents to the cervical sympathetic centers and ganglia have

led to hemiatrophy. Distribution of the postganglionic fibers of the cervical sympathetic ganglia is so extensive that it would account for not only hemiatrophy but also those rare conditions in which atrophy extends into the neck, thorax, and upper limb.

PROGNOSIS

The prognosis is variable. In most cases the course runs for a short period, such as two years, after which it burns out and no further atrophy may occur. In other cases the condition continues longer and may spread to involve other structures.

TREATMENT

Kazanjian and Sturgis[5] advise therapy as follows:

1. Treatment of infections, tumors, congenital cysts of the neck, and bony anomalies of the spinal vertebrae together with treatment of any vasomotor disorder present.
2. Treatment of local disorders while the disease is in progress.
3. Treatment of the facial deformity by fat grafts and dermal grafts after the progress of the disease has ceased. The use of bone or cartilage for grafts is contraindicated, as these are resorbed.

REFERENCES

1. Brain, W. Russell: Diseases of the Nervous System, London, 1955, Oxford University Press.
2. Thoma, K. H.: Oral Pathology, ed. 3, St. Louis, 1950, The C. V. Mosby Company.
3. Archambault, L., and Fromm, N. K.: Progressive Facial Hemiatrophy, A. M. A. Arch. Neurol. & Psychiat. 27: 529, 1932.
4. Muller, L. R.: Zentralbl f. d. ges. Neurol u. Psychiat 25: 490, 1921.
5. Kazanjian, V. H., and Sturgis, S. H.: Surgical Treatment of Hemiatrophy of Face, J. A. M. A. 115: 348, 1940.

IDIOPATHIC RESORPTION WITH METAPLASIA

Report of a Case

Robert Harris, M.D.S. (Syd.), Sydney, Australia*

THE clinical entity of idiopathic resorption has received the attention of various writers, and recently Sullivan and Jolly[1] carefully examined material from a number of patients.

The case reported below is one in which I was fortunate in being able to trace through the roentgenographic records and obtain a complete picture of the progress of the lesion.

The patient was a girl, aged 16½ years. During an oral examination on Oct. 23, 1957, a standard roentgenographic survey of her mouth disclosed, in addition to restorations in several posterior teeth, occlusal dental caries in the upper left second molar and the absence of the upper left second premolar. There was an unusual area of radiolucency in the distal aspect of the crown of the upper left first molar (Fig. 1).

The patient had made no complaint of discomfort or pain in the region or on that side of the face, and careful examination failed to disclose any defect accessible with a probe. The upper first molar had an occlusal defect which was repaired with an amalgam restoration on June 20, 1952. Roentgenograms taken of the region on Oct. 15, 1951, and May 13, 1953 (Fig. 2, *A*, *B*, and *C*), show that there was no evidence of a breakdown on the distal surface of the tooth to be seen in a periapical film of the region (Fig. 2, *B*), although a bitewing film (Fig. 2, *A*) made at the same time (Oct. 15, 1951) shows some radiolucency at the gingival limit of enamel and dentine which seems possibly, on a posteriori evidence, to have been the beginning of the lesion. The bitewing film made on May 13, 1953, however, does not disclose this (Fig. 2, *C*). (The original film demonstrates this clearly, but differences in contrast with the other two prevent a good reproduction on the one block.)

On Sept. 28, 1954, during the course of orthodontic treatment, further roentgenograms revealed, on the distal surface gingival to a cemented band, a small radiolucent area depicted by a break in the shadow picture of the enamel (Fig. 3).

The orthodontic treatment was completed, and the patient was not seen again until Oct. 23, 1956, when roentgenograms revealed a large, irregular, radiolucent area which encroached upon the image of the pulp chamber (Fig. 4). The patient did not return for further treatment until Oct. 23, 1957.

The tooth was extracted, and the external appearance is shown in Fig. 5. The mass of soft tissue was firmly adherent to the tooth, and a fine probe disclosed that it penetrated the crown of the tooth. The tooth was then prepared for microscopic examination. The report stated: "Idiopathic resorption with metaplasia over the distal portion of the tooth. The lesion penetrates the distal surface, but no significant cells are to be seen in this area. The pulp does not appear to be invaded, but it is degenerate and contains some denticles. Large amounts of bone are present within the cavity formed."

*Assistant Superintendent and Head of the Department of Preventive Dentistry, United Dental Hospital, Sydney, and Lecturer (Part-time), University of Sydney.

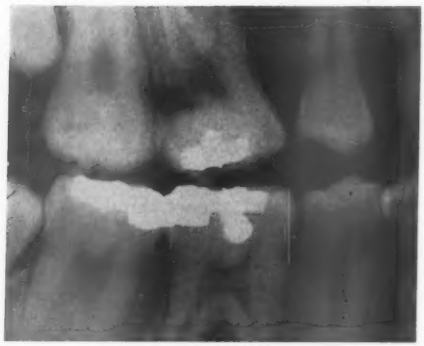


Fig. 1.—Radiolucent area on distogingival aspect of the upper left second molar.

A. *B.* *C.*

Fig. 2.—Roentgenograms of region made Oct. 15, 1951 (*A* and *B*) and June 20, 1952 (*C*). Note absence of upper left second premolar.

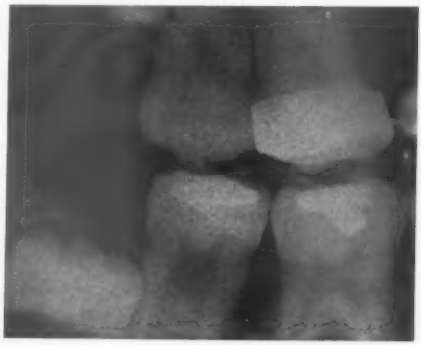


Fig. 3.—Radiolucent area seen on distal surface of upper left second molar gingival to the cemented orthodontic band.

Fig. 4.—Bitewing film of region after completion of orthodontic treatment.

Fig. 5.—Distal surface of tooth showing attachment of soft tissue and area of resorption (*A*).

A significant factor is the absence of any pain, either in the area or referred to other branches of the fifth cranial nerve. It is possible that the lesion may have been present for quite some time and that the restoration of the tooth was a factor which stimulated the growth of the process.[2] The use of the tooth as an anchorage in the orthodontic treatment would seem to have played no part in the process.

The case is interesting in that it has permitted a record to be made of the time factor involved in the establishment and development of the lesion. The fact that it was first detected with certainty on roentgenograms taken at the time of orthodontic treatment indicates the need for careful scrutiny of films for the presence of such defects in the teeth prior to treatment. The rapidity with which the lesion progressed should be noted.

REFERENCES

1. Sullivan, H. R., and Jolly, M.: Idiopathic Resorption, Australian Dent. J. 2: 193-199, 1957.
2. Warner, A. R., Orban, B., Hine, M. K., and Ritchey, B. T.: Internal Resorption of Teeth; Interpretation of Histologic Findings, J. Am. Dent. A. 34: 468-483, 1947.

ENDODONTICS

The American Association of Endodontists

Victor H. Dietz, Editor

. . . . . .

REPARATIVE DENTINOGENESIS

Samuel Seltzer, D.D.S., Philadelphia, Pa.

REPAIR of a bone injury, such as a fracture, is brought about chiefly by the proliferation and differentiation of the osteogenic cells near the bone surfaces. Callus formation and the formation of new bone then occur. In the dental pulp analogous activities follow injury. The eventual result is the formation of reparative dentine, unless almost total necrosis of the pulp intervenes. This article will attempt to explore the mechanism whereby the formation of reparative dentine occurs.

The connective tissue of the dental pulp is normally composed of cells and intercellular substances (fibers embedded in ground substance). The ground substance is an amorphous, gel-like material composed to a great extent of mucopolysaccharides (hyaluronic acid, chondroitin sulfuric acid, and others). These are polymers which give the pulp its viscosity. Collagen and reticular fibers are embedded in the ground substance. The pulp includes fibroblasts, defense cells, and some highly differentiated connective tissue cells, the odontoblasts. Each odontoblast sends a process into the dentine. Thus, exposure of the dentine by dental caries, operative procedures, or other means invariably injures the odontoblasts. These are the first pulp cells to be affected. Products liberated by the injured odontoblasts initiate inflammation in the connective tissue of the dental pulp.

Injury of the odontoblasts is revealed in tissue sections by early morphologic changes. Included among these changes are swelling and loss of distinctiveness of nuclear outlines. Pyknosis, karyorrhexis, or karyolysis of nuclei, indicative of cellular degeneration, may occur.

Presented at the annual meeting of the American Association of Endodontists, Chicago, Illinois, Feb. 6, 1959.

From the Department of Oral Pathology and Oral Histology, School of Dentistry, University of Pennsylvania.

Experiments of the author quoted in this paper were supported by a research grant (D517) from the United States Public Health Service, National Institutes of Health, Bethesda, Maryland.

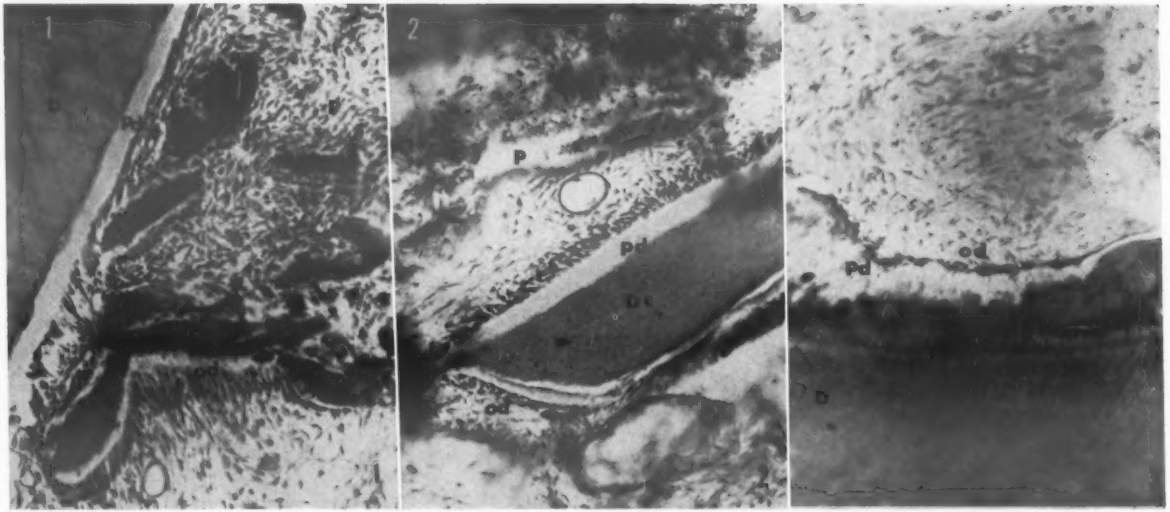


Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—Photomicrograph of transverse section of lower left cuspid of a dog. New odontoblasts (*od*), differentiated from other pulp cells, have secreted matrix around dentine chips. These chips were pushed into the pulp as a result of operative exposure. The pulp was then treated with a suspension of alkaline phosphatase. *D*, Original dentine. *Pd*, Primary dentine. *P*, Pulp. (Magnification, ×180; reduced 3/10.)

Fig. 2.—Photomicrograph of transverse section of lower left carnassial tooth of a dog. Large dentine chips (*Dc*) have been pushed into the pulp (*P*) as a result of operative exposure. The pulp was treated with physiologic saline solution. Original odontoblasts are still aligned on predentine (*pd*). Newly differentiated odontoblasts (*od*), oriented in opposite direction of dentinal tubules, have secreted matrix. (Magnification, ×180; reduced 3/10.)

Fig. 3.—Photomicrograph of buccolingual section of human upper right first premolar. Note flattened odontoblasts (*od*) lining reparative dentine (*pd*). *D*, Dentine. *P*, Pulp. (Magnification, ×180; reduced 3/10.)

Arrangement of the odontoblasts also may be altered from their regular, parallel, palisaded appearance, so that they appear disoriented and no longer parallel or in continuous contact.

The width of the odontoblastic layer may be reduced as a result of the reduced size and number of odontoblasts.

Another striking, but as yet not understood, phenomenon which often occurs in odontoblastic injury is aspiration or migration of the odontoblastic nuclei into the dentine.

Damage to the odontoblasts produces a characteristic interruption in the continuity of the pulpodentinal membrane which separates the cell bodies of the odontoblasts from the predentine.

Detectable vascular changes within the odontoblastic layer are the appearance of dilated, more numerous capillaries which extend to the predentine. Edema may be manifested by the appearance of spaces between the odontoblasts. Erythrocytes may be found between the odontoblasts as a result of hemorrhage. Polymorphonuclear leukocytes also may be detected within the capillaries or between the odontoblasts.

MATRIX-FORMING CELLS

The injured cells may recover, but in all probability most undergo necrosis. Within a few weeks, cellular debris or the dead cells themselves are no longer visible, having been encased in new matrix, the predentine, or by calcified intercellular substance. Hence, the elaboration of this new matrix must come from odontoblasts which have differentiated from other mesenchymal pulp cells or from fibroblasts which have the potentiality of elaborating dentine matrix. That other pulp cells are capable of elaborating dentine matrix was demonstrated recently by Seltzer and Bender[19] in an investigation of the local effects of alkaline phosphatase on exposed dental pulp tissue. They found that fibroblasts became oriented around dentine chips which had been pushed into the pulp following exposure. Dentine matrix was formed abundantly in those pulps which were treated with alkaline phosphatase (Fig. 1). A small amount of matrix was also formed in exposed pulps which were not treated with enzymes (Fig. 2). Thus, the pulpal connective tissue is a reservoir for the continuous supply of dentine matrix-forming cells throughout the life cycle of the dental pulp.

The cells lining reparative dentine more often have a cuboidal shape or the flattened appearance of fibroblasts rather than the columnar shape of odontoblasts (Fig. 3). After the initial injury to the pulp, however, the fibroblasts or other mesenchymal cells hypertrophy and tend to assume a columnar shape. The elaboration of dentine matrix now appears to become their primary function. These cells are strongly basophilic, showing the presence of ribose nucleoproteins.[12] These indicate that active synthesis of extracellular materials is going on.

The new odontoblasts or matrix-forming cells also have many metachromatic cytoplasmic granules. These granules contain both protein and mucopolysaccharide, possibly of the hyaluronic acid type, and they also appear to contain alkaline phosphatase, among other enzymes.[12] The alkaline phosphatase activity has been shown to be much greater in the odontoblasts than in other pulp cells.[7, 23]

FORMATION OF DENTINE MATRIX

The pulp cells secrete collagen precursors.[8] These are probably nonfibrous, incomplete molecules which are secreted into the extracellular ground substance where polymerization to fibrils occurs.[10] The collagen precursors found within the cells are nonsulfated aminopolysaccharides associated with protein. When they leave the cells, they become sulfated. Sulfation may play a part, therefore, in the transformation of precursors into the characteristic matrix (predentine).[11] Leblond, Bélanger, and Greulich[15] reported that dentine matrix is usually composed of a sulfated polysaccharide, as demonstrated by radioautography. Sognnaes,[22] however, pointed out that the appearance of internally administered radiosulfur in dentine, cannot be attributed solely to the presence therein of a sulfated mucopolysaccharide.

Seltzer and Bender[18] have also demonstrated an apparent relationship between the elaboration of fibrous protein (predentine) and phosphatase activity. The elaboration of dentine matrix in layers proceeds continuously, as demonstrated by separation of a C^{14}-labeled matrix layer by an increasingly thick layer of unlabeled matrix as circulating C^{14} glucose decreases.[13]

All collagenous substances contain small amounts of carbohydrates,[5] as well as two or three different mucoproteins or mucopolysaccharide components.[2] The increase of mucopolysaccharides during the repair phase of injury,[6] their sulfation,[21] and/or the increase of alkaline phosphatase activity, apparently makes the matrix capable of binding minerals, thus leading to calcification.

Anderson[1] demonstrated in vitro that the polysaccharides hyaluronic acid, chondroitin sulfate, and heparin bind cations. However, calcium ions were bound by heparin and chondroitin sulfate but not by hyaluronic acid.

The collagen fibrils of dentine may thus be visualized as being coated with sulfated polysaccharides. There is then an attraction for mineral salts. Initially there is an intense metachromasia, but as calcification takes place metachromasia disappears.[14] This coincides with the initial abundance of radiosulfate in nonmineralized areas (predentine) and the subsequent disappearance of the sulfate-tagged substance as the matrix became calcified.[3] However, the precise reason for the attraction of calcium salts to the matrix is not as yet known.

MINERALIZATION OF THE MATRIX

Calcification is an enzyme-controlled phenomenon. Regions of actively calcifying dentine, bordering on the predentine, show the most intense esterase

reaction histochemically. This is correlated with microradiographic findings.[16] The enzyme alkaline phosphatase, which is elaborated by odontoblasts, may thus be involved in calcification. It may split phosphoric esters so that free phosphate ions are liberated. These react with calcium ions to form a precipitate within the matrix. It probably assists in making the dentine matrix calcifiable.

INTERFERENCE WITH MATRIX FORMATION AND CALCIFICATION

When pulpal inflammation is severe, there may be interference with both the elaboration and the calcification of the predentine. Then no dentine is formed (Fig. 4).

Temporary interferences with mineralization, such as those which occur at birth, result in incompletely calcified dentine which appears as the so-called "neonatal line."[17] Operations on the dentine, with resultant damage to the involved odontoblasts, also cause temporary derangements in calcification, shown by the formation of a basophilic line. This has been denoted as a "calciotraumatic" response[9] (Fig. 5).

In other injuries, such as those produced by fluorosis,[4] elaboration of matrix continues, but calcification is interfered with, resulting in irregular and widened predentine and poorly calcified dentine. This may be associated with an initial increased synthesis of chondroitin sulfate.

Severe irritation may cause such rapid elaboration of matrix that the tubular structure may become lessened or tortuous, or it may even disappear. At times, cells or blood vessels may be surrounded and engulfed by the rapidly formed ground substance. The dentine thus formed is known as "osteodentine" because of its bonelike appearance (Fig. 6).

NUTRITIONAL INFLUENCES

Both matrix formation and calcification are influenced by various nutritional deficiencies (hormones, vitamins) and other systemic factors. Shaw[20] listed many nutritional factors which affect the bones and teeth. With respect to dentine formation, the following deficiencies seemed significant:

> Vitamin A deficiency in rats and guinea pigs produced failure of the pulp cells to differentiate into odontoblasts. The characteristic alignment of the odontoblasts was lost. Hence, dentine formation was irregular and occurred in varying amounts.
>
> Ascorbic acid deficiency interfered with the formation of intercellular substances throughout the body. Odontoblasts failed to deposit predentine. They became atrophic and soon resembled nearby pulp cells. Eventually they were completely disorganized. Therefore, dentine was laid down irregularly and at a greatly reduced rate. The dentinal tubules were arranged in haphazard fashion. In severe deficiencies, dentine deposition soon stopped entirely and the predentine became hypercalcified. Replacement dentine was of the osteodentine type.

Fig. 4. Fig. 5 Fig. 6.

Fig. 4.—Photomicrograph of buccolingual section of human upper left first premolar. Pulp (*P*) has become inflamed following placement of silicate restoration on dentine (*D*). Predentine (*pd*) has been formed in one region but is absent in another (*X*). (Magnification, ×180; reduced ⅓₀.)

Fig. 5.—Photomicrograph of labiolingual section of upper left canine of dog. Cavity had been prepared in dentine (*D*) three months earlier. The dentine shows a calciotraumatic response (*cr*). The odontoblasts (*od*) are reduced in size in one region (*X*) of pulp (*P*). (Magnification, ×55; reduced ⅓₀.)

Fig. 6.—Photomicrograph of labiolingual section of a lower right canine of a dog. The pulp had been exposed mechanically with a bur. It was then touched with a red-hot wire. Five months later osteodentine (*OsD*) was abundantly present in the pulp canal (*P*). *D*, Original dentine. (Magnification, ×55; reduced ⅓₀.)

Vitamin D deficiency caused disturbed calcification in the dentine. The formation of predentine was retarded and calcification was interfered with, so that there was an irregular deposition of inorganic salts.

Thus, the formation of dentine appears to be influenced by systemic as well as local factors. All connective tissues are affected by hormones, but it is not yet clear how reparative dentinogenesis is specifically influenced.

SUMMARY AND CONCLUSIONS

Data from recent studies of the biochemistry of collagen and bone formation have been reviewed, and an attempt has been made to integrate these with our understanding of dentinogenesis. While it is true that some of the studies are directly related to bone or collagen, inferences have been drawn which seem reasonable. The formation of dentine seems to follow essentially the pattern of the formation of bone and other hard tissues.

Progress in our further understanding of dentinogenesis rests fundamentally on our understanding of the biochemical activities of the cells concerned. These cells (the matrix formers) are connective tissue cells, the odontoblasts, and the less differentiated fibroblasts. It seems reasonably certain that any mesenchymal pulp cell can assume the function of forming dentinoid. It accomplishes this by synthesizing cytoplasmic granules (collagen precursors). It then secretes extracellularly these granules, which contain aminopolysaccharides associated with proteins. During this process they become sulfated. The collagen fibrils which make up the predentine are coated with a sleeve of sulfated polysaccharides. Alkaline phosphatase also appears to be involved in this process of matrix formation. Finally, mineral salts are attracted to the matrix and calcification ensues, resulting in the formation of mature dentine.

The steps in reparative dentine formation may be summarized as follows: (1) injury to the odontoblasts; (2) inflammatory response; (3) differentiation of new odontoblasts or matrix-forming cells; (4) synthesis of cytoplasmic granules (collagen precursors); (5) secretion of collagen precursors (nonsulfated aminopolysaccharides associated with proteins); (6) sulfation of aminopolysaccharide, complexed with protein; (7) formation of collagen fibrils (matrix); and (8) attraction of mineral salts (calcification).

REFERENCES

1. Anderson, D. L.: In Vitro Binding of Cations by Tissue Polysaccharides (Abst.), J. D. Res. **37**: 42, 1958.
2. Banga, I., and Balo, J.: The Structure and Chemical Composition of Connective Tissue. In Connective Tissue, a Symposium, Oxford, 1957, Blackwell Scientific Publications.
3. Bélanger, L. F.: Autoradiographic Studies of the Formation of the Organic Matrix of Cartilage, Bone and the Tissues of Teeth. In CIBA Foundation: Bone Structure and Metabolism, Boston, 1956, Little, Brown & Company.
4. Bélanger, L. F., Visek, W. J., Lotz, W. E., and Comar, C. L.: The Effects of Fluoride Ingestion on the Organic Matrix of the Teeth of Growing Pigs, J. D. Res. **37**: 264, 1958.
5. Grassman, W., Hofman, U., Kühn, K., Hörmann, H., Endres, H., and Wolf, K.: Electron Microscope and Chemical Studies of the Carbohydrate Groups of Collagen, Connective Tissue, a Symposium, Oxford, 1957, Blackwell Scientific Publications.

6. Gillman, T., Hathorn, M., and Penn, J.: Micro-Anatomy and Reactions to Injury of Vascular Elastic Membranes and Associated Polysaccharides, Connective Tissue, a Symposium, Oxford, 1957, Blackwell Scientific Publications.
7. Greep, R. O., Fischer, C. J., and Morse, A.: Alkaline Phosphatase in Odontogenesis and Osteogenesis and Its Histochemical Demonstration After Demineralization, J. Am. Dent. A. **36**: 427, 1948.
8. Gross, J.: Studies on the Fibrogenesis of Collagen. Some Properties of Neutral Extracts of Connective Tissue, Connective Tissue, a Symposium, Oxford, 1957, Blackwell Scientific Publications.
9. Irving, J. T., and Weinman, J. P.: Experimental Studies in Calcification. VI. Response of Dentin of the Rat Incisor to Injection of Strontium, J. D. Res. 27: 669, 1948.
10. Jackson, D. S.: The Formation and Breakdown of Connective Tissue, Connective Tissue, a Symposium, Oxford, 1957, Blackwell Scientific Publications.
11. Jackson, S. F., and Randall, J. T.: Fibrogenesis and the Formation of Matrix in Developing Bone. In CIBA Foundation: Bone Structure and Metabolism, Boston, 1956, Little, Brown & Company.
12. Jackson, S. F.: Structural Problems Associated With the Formation of Collagen Fibrils *In Vivo*, Connective Tissue, a Symposium, Oxford, 1957, Blackwell Scientific Publications.
13. Kumamoto, Y., and Leblond, C. P.: Visualization of C^{14} in the Tooth Matrix After Administration of Labeled Hexoses, J. D. Res. **37**: 147, 1958.
14. Lacroix, P.: The Histological Remodelling of Adult Bone; An Autoradiographic Study. In CIBA Foundation: Bone Structure and Metabolism, Boston, 1956, Little, Brown & Company.
15. Leblond, C. P., Bélanger, L. F., and Greulich, R. C.: Formation of Bones and Teeth as Visualized by Radioautography, Ann. New York Acad. Sc. **60**: 631, 1955.
16. Savchuck, W. B., and Burstone, M. S.: Calcification and Esterase Localization in Developing Dentin (Abst.), J. D. Res. **37**: 5, 1958.
17. Schour, I., and Massler, M.: The Neonatal Line in Enamel and Dentin of the Human Deciduous Teeth and First Permanent Molar, J. Am. Dent. A. **23**: 1946, 1936.
18. Seltzer, S., and Bender, I. B.: Some Factors Affecting Repair of Exposed Pulps in Dogs' Teeth, ORAL SURG., ORAL MED. & ORAL PATH. **37**: 678, 1958.
19. Seltzer, S., and Bender, I. B.: Alkaline Phosphatase in Reparative Dentinogenesis (unpublished data).
20. Shaw, J. H.: Effect of Nutritional Factors on Bones and Teeth, Ann. New York Acad. Sc. **60**: 733, 1955.
21. Sobel, A. E.: Local Factors in the Mechanism of Calcification, Ann. New York Acad. Sc. **60**: 713, 1955.
22. Sognnaes, R. F.: Microstructure and Histochemical Characteristics of the Mineralized Tissues, Ann. New York Acad. Sc. **60**: 713, 1955.
23. Wislocki, G. B., and Sognnaes, R. F.: Histochemical Reactions of Normal Teeth, Am. J. Anat. **87**: 239, 1950.

2035 SPRUCE ST.

RESEARCH

. . . . . .

THE RESPONSE OF SELECTED ORAL TISSUES TO SOMATOTROPIC HORMONE IN RATS FED A PROTEIN-FREE DIET

S. S. Stahl, D.D.S., M.S., R. Gerstner, Ph.D., and O. Joly, D.D.S.,
New York, N. Y.

GROWTH of oral tissues has been stimulated by the administration of somatotropic hormone (STH).[1-5] The present study was undertaken in order to observe the response of oral tissues to STH in rats fed a protein-free diet.

MATERIAL AND METHODS

Forty male rats of the Long-Evans strain, weighing an average of 250 grams each at the beginning of the experiment, were divided into four groups. Group I consisted of fifteen animals fed a protein-free diet* ad libitum and given intraoral subcutaneous injections of 0.5 mg. of STH buffered to a pH of about 10 in 0.1 c.c. of distilled water three times weekly over a six-week period. Group II consisted of ten animals fed a protein-free diet ad libitum and given subcutaneous injections of the vehicle in the same manner as outlined for Group I. Group III consisted of ten animals fed a protein-free diet ad libitum for a six-week period. Group IV consisted of five animals kept as untreated controls.

At the end of the experimental period, the site of injection, the maxilla, and the femur were dissected out and prepared for histologic study.

GROSS OBSERVATIONS

The animals on the protein-free diet reduced their food intake as the study progressed and were thus on partial inanition during the experimental period. At the end of six weeks, these animals had lost approximately one-half their

From the Murry and Leonie Guggenheim Foundation, Institute for Dental Research, and the Departments of Periodontia, Oral Medicine, and Anatomy, New York University College of Dentistry.

This study was supported in part by grant-in-aid D-537 from the National Institute for Dental Research of the National Institutes of Health, Bethesda, Maryland. Growth hormone was obtained through a gift from the Endocrinology Study Section, National Institutes of Health.

*Protein-free diet was obtained from Nutritional Biochemical Company, Cleveland, Ohio.

initial body weight. STH-treated animals on a protein-free diet also exhibited a marked weight loss, which was not significantly different from the weight loss seen in the groups on a protein-free diet alone.

HISTOLOGIC OBSERVATIONS

The epithelium of STH-treated oral mucosa from protein-deprived animals showed an acanthosis with increased keratinization and rete peg proliferation. The individual epithelial cells appeared to be increased in size, and many were binucleated (Fig. 4). No increase in mitotic figures was noted in the germinal layer. The underlying connective tissue stained paler than normal but appeared to be more cellular than the subcutaneous connective tissue seen in the control animals.

Injections of the vehicle did not lead to an enlargement of the epithelial layer and did not show the frequent binucleation seen in the STH-treated specimens (Figs. 1, 2, 3, and 4). An inflammatory infiltrate in the subepithelial structures was seen more frequently in the vehicle-treated group than in the STH-treated animals.

The periodontal structures of STH-treated animals fed a protein-free diet showed marked differences when compared to the control groups. Protein deprivation led to an osteoporosis and reduction in cellularity of the periodontal membrane in both the vehicle-injected, protein-free fed group and the group fed a protein-free diet alone. STH appeared to inhibit this osteoporosis (Figs. 5, 6, 7, and 8). The periodontal membrane of the STH-treated group showed a greater cellularity and more collagen bundles than were observed in the control groups fed a protein-free diet (Figs. 9 and 10). The epithelial attachment was at the level of the cementoenamel junction in all animals studied.

A loss of bone trabeculae was noted in both diaphysis and epiphysis of the femur in the vehicle-injected animals fed a protein-free diet as well as in the animals fed a protein-free diet alone. STH administration seemed to inhibit this loss of trabeculae (Figs. 11 and 12).

COMMENT

The present findings indicate that, under the experimental conditions outlined, STH administration in protein-depleted rats was unable to prevent the weight loss associated with this type of dietary deficiency. STH administration, however, was able to maintain and possibly stimulate osteogenesis in the alveolar bone and femur and also to maintain the structure of the periodontal membrane. These findings are in essential agreement with those of Bavetta, Bernick, and Ershoff, who demonstrated similar maintenance of osteogenesis and chondrogenesis in tryptophan-deficient rats receiving STH.[6] They postulated that "(1) chondrogenesis and osteogenesis may be more sensitive than increment in body weight as an index of growth hormone activity or (2) the dietary deficiency of tryptophan might interfere with one manifestation of growth hormone activity (i.e., increment in body weight) whereas another might remain relatively unimpaired." This latter concept might now be extended to include

total protein deprivation, since STH administration in total-protein-deprived animals also exerted a sparing effect on bone. The maintenance of the collagen fibers of the periodontal membrane further suggests that other connective tissue elements may also be affected by the sparing action of STH in these deprived animals and may be the result of the ability of STH to promote nitrogen retention and protein anabolism.[7-9]

Fig. 1. Fig. 2.

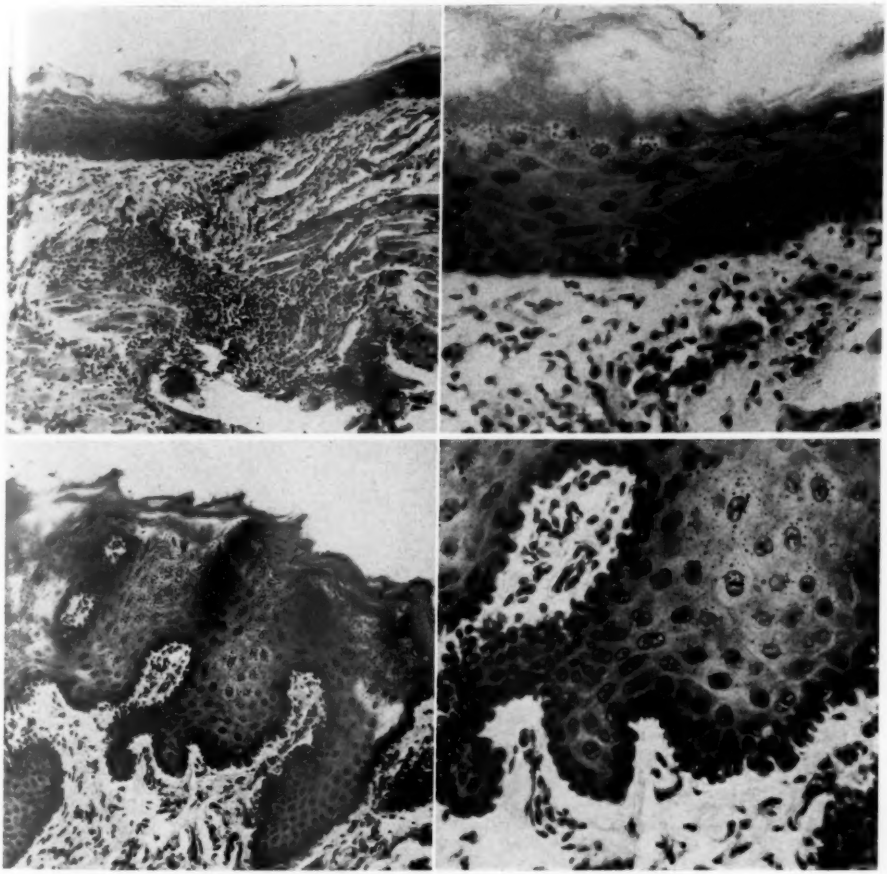


Fig. 3. Fig. 4.

Fig. 1.—Photomicrograph of a section of oral mucosa from a vehicle-injected rat fed a protein-free diet for six weeks. Note the over-all appearance of the epithelial layer and the inflammatory infiltrate in the connective tissue. (Hematoxylin and eosin stain. Magnification, ×100; reduced ⅕.)

Fig. 2.—Higher magnification of the specimen shown in Fig. 1. (Hematoxylin and eosin stain. Magnification, ×400; reduced ⅕.)

Fig. 3.—Photomicrograph of a section of oral mucosa from an STH-injected rat fed a protein-free diet for six weeks. Note the acanthosis of the epithelium and the large number of binucleated cells present in the prickle-cell layer. (Hematoxylin and eosin stain. Magnification, ×150; reduced ⅕.)

Fig. 4.—Higher magnification of the specimen shown in Fig. 3. (Hematoxylin and eosin stain. Magnification, ×350; reduced ⅕.)

The oral epithelial response following STH administration in protein-depleted rats was similar to that seen in STH-treated oral mucosa of rats on a normal laboratory diet,[4] but it appeared to be of lesser magnitude. Since the

Fig. 5 Fig. 6.

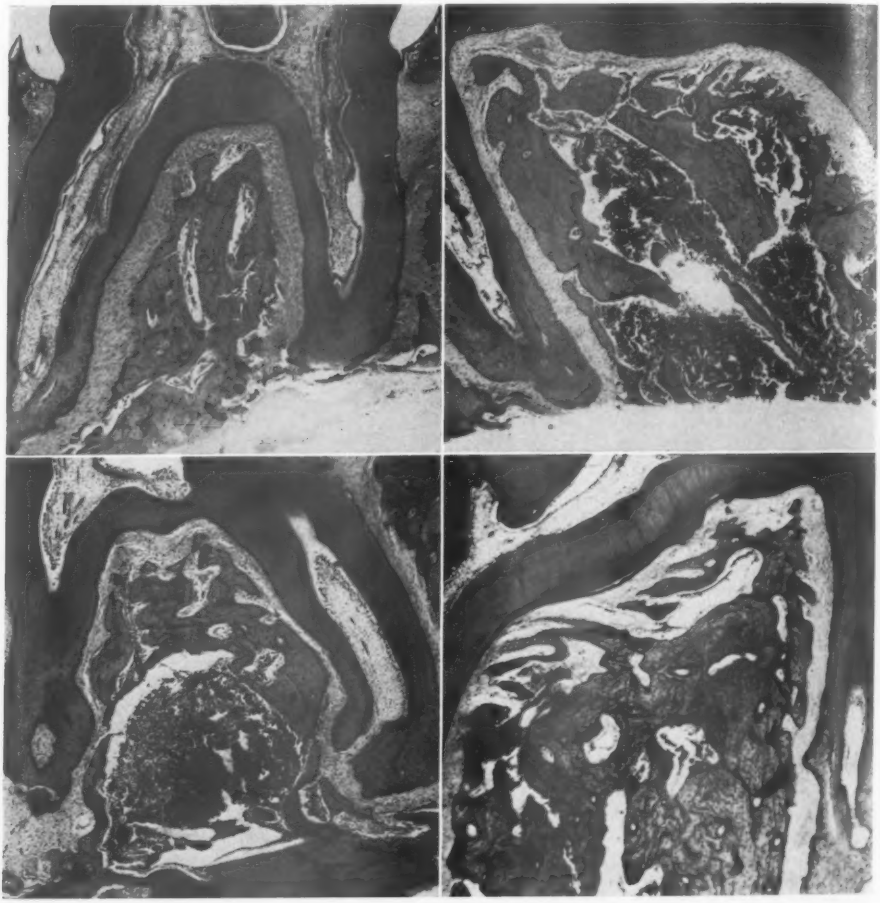


Fig. 7. Fig. 8.

Fig. 5.—Photomicrograph of a mesiodistal section of the first maxillary molar of a non-treated control rat. (Hematoxylin and eosin stain. Magnification, ×40; reduced ⅕.)

Fig. 6.—Photomicrograph of a mesiodistal section of the first maxillary molar of a rat on a protein-free diet for six weeks. Note the markedly enlarged interradicular marrow spaces. (Hematoxylin and eosin stain. Magnification, ×40; reduced ⅕.)

Fig. 7.—Photomicrograph of a mesiodistal section of the first maxillary molar of a vehicle-injected rat on a protein-free diet for six weeks. Note the enlarged interradicular marrow spaces. (Hematoxylin and eosin stain. Magnification, ×40; reduced ⅕.)

Fig. 8.—Photomicrograph of a mesiodistal section of the first maxillary molar of an STH-injected rat on a protein-free diet for six weeks. Note the reduced size of the interradicular marrow spaces as compared with specimens shown in Figs. 6 and 7. (Hematoxylin and eosin stain. Magnification, ×40; reduced ⅕.)

epithelial response was essentially limited to the site of injection, it supports evidence regarding a possible direct effect of STH on individual cells as postulated by Moon and St. Vincent.[10]

SUMMARY AND CONCLUSIONS

Young adult male rats placed on a protein-free diet were subjected to oral injections of somatotropic hormone.

Fig. 9.

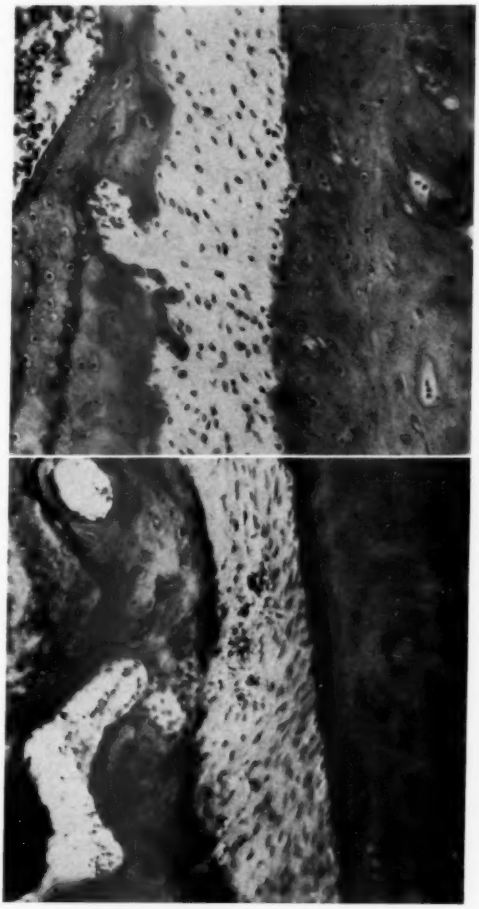


Fig. 10.

Fig. 9.—Photomicrograph of a section of the periodontal membrane of the maxillary first molar of a rat fed a protein-free diet for six weeks. Note the reduction in cellularity of the periodontal membrane. (Hematoxylin and eosin stain. Magnification, ×120; reduced ⅙.)

Fig. 10.—Photomicrograph of a section of the periodontal membrane of the maxillary first molar of an STH-injected rat fed a protein-free diet for six weeks. Note the increased cellularity of this periodontal membrane as compared to the section shown in Fig. 9. (Hematoxylin and eosin stain. Magnification, ×120; reduced ⅙.)

1. The oral epithelium at the site of injection showed an acanthosis and an increase in binucleated cells in the prickle-cell layer.

2. STH administration inhibited the osteoporotic changes in both the alveolar bone and the femur observed in the control groups fed a protein-free diet. The periodontal membrane of the STH-treated group showed greater cellularity than was observed in the periodontal membrane of animals fed a protein-free diet alone.

Fig. 11.

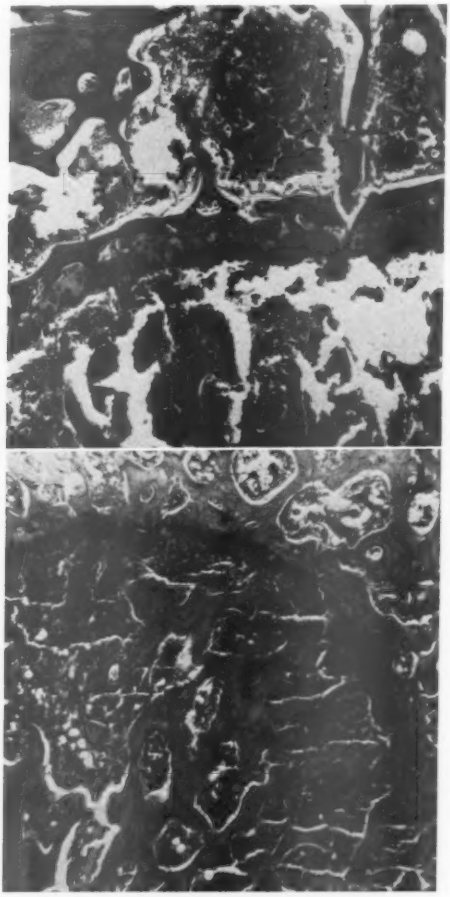


Fig. 12.

Fig. 11.—Photomicrograph of a section of the head of the femur of a vehicle-injected rat fed a protein-free diet for six weeks. Note the loss of trabeculae. (Hematoxylin and eosin stain. Magnification, ×50; reduced ⅕.)

Fig. 12.—Photomicrograph of a section of the head of the femur of an STH-injected rat fed a protein-free diet for six weeks. Note the increase in trabeculae seen in this specimen as compared to the specimen shown in Fig. 11. (Hematoxylin and eosin stain. Magnification, ×50; reduced ⅕.)

3. STH administration did not prevent the over-all weight loss which took place following administration of a protein-free diet.

REFERENCES

1. Becks, H., Collins, D. A., Simpson, M. E., and Evans, H. M.: Growth and Transformation of Mandibular Joint in the Rat; Effect of Growth Hormone and Thyroxin Injections in Hypophysectomized Female Rats, Am. J. Orthodontics & Oral Surg. **32**: 447, 1946.
2. Baume, L. J., Becks, H., and Evans, H. M.: Hormonal Control of Tooth Eruption. III, J. D. Res. **33**: 105, 1954.
3. Mackenzie, R., and Avery, J. K.: Investigation of Localized Action of Somatotropin on the Temporomandibular Joint, J. D. Res. **37**: 81, 1958.
4. Stahl, S. S., Gerstner, R., and Joly, O.: The Effects of Local Injections of Somatotropic Hormone in Small Doses Into the Oral Mucosa of Young Adult Rats, J. D. Res. **37**: 280, 1958.
5. Stahl, S. S., and Joly, O.: The Response of Periodontal Tissues to Injections of Somatotropic Hormone, ORAL SURG., ORAL MED. & ORAL PATH. **11**: 475, 1958.
6. Bavetta, L. A., Bernick, S., and Ershoff, B. H.: Selective Effects of Growth Hormone on Rats Fed a Tryptophan-Low Diet, Endocrinology **58**: 701, 1956.
7. McHenry, E. W.: Importance of the Nutritional State for the Biologic Function of Growth Hormone. In Smith, R. W., Gaebler, O. H., and Long, C. N. H.: The Hypophyseal Growth Hormone, Nature and Actions, New York, 1955, McGraw-Hill Book Company, Inc.
8. Bennett, L. L., Li, C. H., and Laundrie, B.: Production of Nitrogen Retention in Hypophysectomized Rats by Small Doses of Hypophyseal Growth Hormone, Proc. Soc. Exper. Biol. & Med. **68**: 94, 1948.
9. Li, C. H., Simpson, M. E., and Evans, H. M.: Influence of Growth and Adrenocorticotrophic Hormones on the Body Composition of Hypophysectomized Rats, Endocrinology **44**: 71, 1949.
10. Moon, R. W., and St. Vincent, L.: Effect of Somatotropin on Cells in Tissue Culture, Science **125**: 643, 1957.

Section by the

ARMED FORCES AND PUBLIC HEALTH SERVICE

METABOLIC STUDIES OF HUMAN ALVEOLAR BONE DISEASE

I. Nitrogen, Calcium and Phosphorus Balances

Philip Person, D.D.S., Ph.D., Brooklyn, N. Y.*

INTRODUCTION

DETERMINATION *of Metabolic Balances in Patients With Bone Disease.*—In recent years, metabolic balance studies in patients with bone disease have greatly increased our knowledge and understanding of dynamic equilibria involving calcium, protein, and phosphorus, and of their interaction in bone physiology and pathology.[1, 2] A principal contribution of such studies has been improvement in methods for evaluation and management of the bone diseases that Albright and his associates[2] classified as *osteoporoses.* These workers postulated that in osteoporoses disturbances in tissue protein metabolism result in insufficient bone matrix formation. By way of contrast, in the disorders classified as *osteomalacias,* protein metabolism was believed to be unimpaired, and the primary fault was thought to be one of mineral metabolism.

A feature of the osteoporoses studied by Albright, and since confirmed by others, was the existence of a negative nitrogen (protein) balance in many patients. The osteoporoses were of diverse etiology (postmenopausal, Cushing's syndrome, atrophy of disuse, posttraumatic, etc.). In many instances, when shifts to positive nitrogen balance could be produced, there was an accompanying improvement in the condition of the patient.† The attainment of positive

From the Special Dental Research Program, the Dental Service, and the Metabolism Research Ward, Veterans Administration Hospital, Brooklyn, New York.

*Chief, Special Dental Research Program, Veterans Administration Hospital, Brooklyn, New York; Associate Professor of Biochemistry, Bureau of Biological Research, Rutgers University, New Brunswick, New Jersey.

†A negative nitrogen balance exists when *more* nitrogen is excreted from the body than is absorbed by it. The body possesses no nitrogen (or protein) stores in the sense that it does fat and carbohydrate stores. Therefore, a negative nitrogen balance implies a breakdown of cell and tissue protoplasm in actively metabolizing structures as the source of the excess excreted nitrogen. A positive nitrogen balance, on the other hand, exists when the individual excretes *less* nitrogen than is absorbed. This indicates retention of nitrogen by the body for use in the synthesis of cell proteins.

nitrogen balance was, in certain cases, enhanced by increased protein intake and the administration of estrogen and androgen substances which stimulate protein anabolism. It should be stressed that in most osteoporoses, in contrast to the osteomalacias, customary clinical determinations for serum calcium, phosphorus, and alkaline phosphatase remain essentially unchanged from average values, even while profound metabolic shifts may be occurring within the patient. Lack of alteration of these entities (that is, serum calcium, phosphorus, and alkaline phosphatase) has been interpreted to indicate that tissue protein metabolism, and not mineral metabolism, is disturbed in osteoporosis. Without the use of balance techniques, therefore, it would be almost impossible to follow the metabolic changes in patients with osteoporosis.

Studies of the Effects of Disturbances in Protein Metabolism Upon Alveolar Bone in Animals.—As the importance of the role of protein metabolism in reactions of bone became increasingly evident from studies by the Albright group and others, workers in dental research expressed interest in the possible influences of protein metabolism upon specific oral structures. A number of independent investigations were undertaken to determine the extent to which alveolar bone and other oral tissues were affected by disturbances in protein metabolism. Experiments involving restriction of protein intake in rats and monkeys,[3-9] and of amino acid intake in rats[10, 11] demonstrated that a generalized osteoporosis is produced and that alveolar bone participates with other portions of the skeleton in the metabolic adjustments to the above forms of inanition. Gonadal endocrine factors capable of influencing protein metabolism have also been studied and have been shown to be capable of producing generalized skeletal changes which involve alveolar bone in rats and mice.[12-16] Interesting and significant species differences in bone responses to gonadal hormone factors were demonstrated in certain of these studies.[12, 14] The net result of the researches listed above has been to demonstrate that under experimental conditions of protein and amino acid deprivation, as well as conditions of gonadal hormone imbalances known to affect protein metabolism, alveolar bone metabolism was altered with resulting pathologic changes.

The Need for Metabolic Balance Studies in Patients With Alveolar Bone Diseases.—Questions have been raised concerning the possibility that disturbances of protein metabolism may be involved in certain *clinical* alveolar bone disorders. Some authors have suggested that the alveolar bone loss seen in periodontosis and related severe alveolar bone resorptions may be caused by metabolic disturbances in which there exists or is produced a negative nitrogen balance.[17-19] It has been suggested, too, that the rapid, severe alveolar bone loss seen in many patients with untreated or poorly controlled diabetes may be a result of the intermittent negative nitrogen balance known to exist in such patients.[20, 21] The loss of alveolar bone seen in aged persons also deserves study to determine whether or not such factors as protein malnutrition and diminished gonadal hormone production (both of which may cause negative nitrogen balance) are implicated.

The brief reviews presented in the preceding paragraphs indicate the importance to dentistry of a greater knowledge *at clinical levels* of the influence of

protein metabolism upon oral structures. Such knowledge is particularly needed in relation to certain types of alveolar bone resorption. Obviously, if disturbances in protein metabolism exist in a causal relation to these severe alveolar bone resorptions, dentists will better understand their pathogenesis and a more rational therapy will be closer. A careful review of the literature indicated that clinical studies of protein and related metabolic balances in patients with alveolar bone disease had not yet been made; the present investigations were therefore undertaken.

Nature of Present Studies.—It is the purpose of this article to report metabolic balance studies in relation to human alveolar bone disease. Nine years ago at the Mount Sinai Hospital in New York we made preliminary observations on the relationship between nitrogen balance and oral tissue changes in patients with diabetes mellitus. These observations were not published, since only two cases were involved. More recently, with the establishment of a Special Dental Research Program within the Veterans Administration, it has been possible to extend these observations by means of studies *specifically designed* to investigate nitrogen, calcium and phosphorus metabolism in relation to alveolar bone changes in patients with and without generalized bone disease. In these more recent studies, metabolic balances have thus far been determined in an additional three patients, making a total of five cases studied to date. In the next section of this article organization, plan of studies, materials and methods, and the selection of patients will be discussed. This will be followed by the presentation of cases. For those interested in additional details, we have included an appendix in which is outlined a typical patient study. The appendix also contains a chart summarizing and depicting the over-all organization of these investigations.

To our knowledge, the present studies represent the first carried out in human beings for the specific purpose of correlating metabolic balances with changes in alveolar bone. They represent a beginning effort to gather quantitative data that may aid us in solution of the problems outlined above.

ORGANIZATION AND PLAN OF STUDIES, MATERIALS AND METHODS, AND SELECTION OF PATIENTS

We will outline the organization and plan of studies developed at the Veterans Administration Hospital in Brooklyn. This will permit incorporation of dental considerations not previously described in the literature. We wish to acknowledge a debt to Albright and his associates,[1, 2] whose work was of great value in our planning.

General Plan of a Balance Study.—Without intelligent and willing cooperation on the part of the patient, a meaningful balance determination is difficult and at times impossible.

The amount of time devoted to each study varies. In the group of cases to be presented here, the shortest period was nine days and the longest was ninety days. Based upon our present experience, it is felt that a study should last for a *minimum* of eighteen days, divided into three-day periods. The first

two periods permit orientation of the patient to diet, collection procedures, and special ward routines. The next two periods are employed for control balance determinations. The remaining time may be utilized for introduction of variables which affect metabolism or for performance of special test procedures, such as calcium load tests, renal function tests, etc. An eighteen-day study will permit preliminary evaluation of the problem, and from it the desirability and feasibility of prolonging the investigation can be determined.

Prior to acceptance of the patient on the ward, the dietitian prepared, in frozen form, *all* the food required by the patient for a given study. From a given cut or muscle group of beef, single weighed portions sufficient for the entire study were prepared, wrapped, and kept frozen until used. Similarly, fruits, vegetables, dairy products, bread, etc., were drawn from single sources and weighed or measured into individual portions which were kept frozen until used. Food was cooked and served in the same containers, designed to prevent spillage and loss. Food not eaten was returned to the kitchen; its weight was determined and subtracted from the weight of the original portion. Generally speaking, patients ate everything offered. By these methods, which are standard in such studies, variation in composition of foods was minimized, and the exact amount ingested during each meal was known. In the first two studies (Mt. Sinai Hospital) diet composition was determined by calculations made from standard tables of food composition.[22] In the remaining studies (Veterans Administration Hospital), a typical daily menu was homogenized in a large Waring Blendor, and aliquots were taken for chemical determination of nitrogen, calcium, and phosphorus. Thus, the daily intake of these elements was known. To determine their output, complete daily collections of urine and feces were made and aliquots of these or of pooled samples were analyzed for nitrogen, calcium, and phosphorus. Subtraction of the amount of an element excreted from the amount ingested indicated whether the patient was in negative or positive balance or whether he was in equilibrium, that is, neither gaining nor losing (also referred to as zero balance).

Laboratory Procedures.—Nitrogen was determined by a micro-Kjeldahl procedure,[23] calcium by permanganate titration according to the method of Clark and Collip,[24] and phosphorus by the molybdate method of Fiske and Subbarow.[25] Albumin-globulin ratios were determined by the method of Kingsley,[26] and creatinine by the method of Folin and Wu.[27] Urine was collected in glass cylinders immersed in crushed ice, with toluene as preservative. Feces were collected in aluminum pans, stored in a refrigerator during the collection period, and later stored in the Deep Freeze. Homogenizations of diet and feces were performed with a large-capacity (1 gallon) Waring Blendor. Feces were further homogenized with an Epperbach homogenizer. All chemical determinations were made in duplicate, except for diet and stool samples which were performed in triplicate. Nitrogen balances between +1.5 and –1.5 grams per day are interpreted to indicate nitrogen equilibrium.

Selection of Patients.—Five patients have been studied to date.

The first two patients (Cases 1 and 2) had diabetes mellitus, and both were studied on the Metabolism Research Ward of the Mount Sinai Hospital

in 1948. Each presented a difficult problem in diabetes management. These patients were admitted to the ward in order that the reasons for the marked fluctuations in their insulin requirements might be determined.

Patient S. S. (Case 1) was a 55-year-old diabetic white woman. During her stay on the ward, and while she was on balance study, the extraction of two upper molar teeth was necessary. The effects of this procedure on the nitrogen balance of the patient will be presented in detail.

Patient J. G. (Case 2) was a 64-year-old diabetic white man who was edentulous and wore acrylic dentures. In this patient it was possible to observe gingiva and bone in the absence of periodontal complications and against a background of controlled shifts in metabolic status.

The other three patients (Cases 3, 4, and 5) were studied during the past year as part of the oral tissue metabolism studies of the Special Dental Research Program at the Veterans Administration Hospital in Brooklyn.

Patient R. C. (Case 3), a 60-year-old white man, was admitted because of severe bone resorption involving maxilla, mandible, ribs, and vertebrae. Loosening of the maxillary incisors was the first symptom noticed by the patient; it preceded by approximately two years the appearance of symptoms elsewhere in the body. The nature of the underlying disease process has not yet been determined. Tooth extractions and an alveoloplasty were performed while the patient was on balance study, with results that differed from those seen in the first patient.

Patient S. S. (Case 4) was a 41-year-old white man who was admitted because of severe alveolar bone resorption in the absence of any detectable local intraoral or systemic contributory factors. This case was of great interest, since the rate of alveolar bone loss was very rapid and yet no causes could be found.

Patient W. M. K. (Case 5), a 29-year-old Negro man, was admitted to the ward because of an idiopathic hypoparathyroidism. In this disease, the

TABLE I. PATIENTS REPORTED IN STUDY

PATIENT	AGE	SEX	DIAGNOSIS AND REMARKS
(1) S. S.	55	Female	Diabetes mellitus; fluctuating insulin requirements; study of effects of infection and tooth extraction upon nitrogen balance
(2) J. G.	64	Male	Diabetes mellitus; fluctuating insulin requirements; patient edentulous and wearing dentures; study of effects of variation in insulin intake upon nitrogen balance and oral tissues
(3) R. C.	60	Male	Nondiagnosed resorptive bone disease affecting alveolar bone, ribs, and vertebrae; study of nitrogen, calcium, and phosphorus metabolism; effects of tooth extraction and alveoloplasty upon above
(4) S. S.	41	Male	Severe alveolar bone loss in the absence of detectable local factors or systemic disease; study of nitrogen, calcium, and phosphorus balances
(5) S. M. K.	29	Male	Idiopathic hypoparathyroidism with generalized increase in density of bone, including maxillary and mandibular alveolar bone; study of nitrogen, calcium, and phosphorus balances and their response to therapy

metabolism of the patient is almost the reverse of that seen in hyperparathyroidism. Instead of a high serum calcium and low serum phosphorus, a low serum calcium and an elevated phosphorus are found. Instead of excess excretion of calcium in the urine, the urinary calcium excretion is almost nil. In this patient, alveolar bone was abnormally dense, as seen in intraoral and extraoral roentgenograms. This is a relatively rare disease, infrequently reported in the dental literature, and of considerable teaching value. Hence, correlation of the alveolar bone picture with the patient's metabolic status was of great interest.

The above cases are summarized in Table I.

The above selection of patients represents a spectrum of alveolar bone involvements of interest to the dentist for practical and theoretical reasons. Fortunately, these patients were intelligent and cooperative persons who willingly followed the requirements of each study. Detailed presentation of the results of study of these patients will be made in the section that follows. The material for each case will be organized into three parts: (1) case summary; (2) data, and (3) comments.

CASE REPORTS

Case 1 (Patient S. S., M.S.H. #3318252).—

Case summary: This 55-year-old white woman was a known diabetic for fifteen years and was seen regularly in the outpatient Diabetes Clinic prior to her admission on the Metabolism Research Ward. For several weeks preceding admission, it was noted that her diabetes mellitus was poorly controlled, and attempts to achieve better control were not successful. The patient was placed on the ward in order that reasons for the poor control might be determined. Since details pertaining to other aspects of the metabolism of this patient have been published elsewhere,[28] we will discuss only the metabolic consequences of oral disease as seen in this woman. Pertinent details begin with the tenth day of the study, when the patient complained of severe pains in the upper left molar area. Oral examination

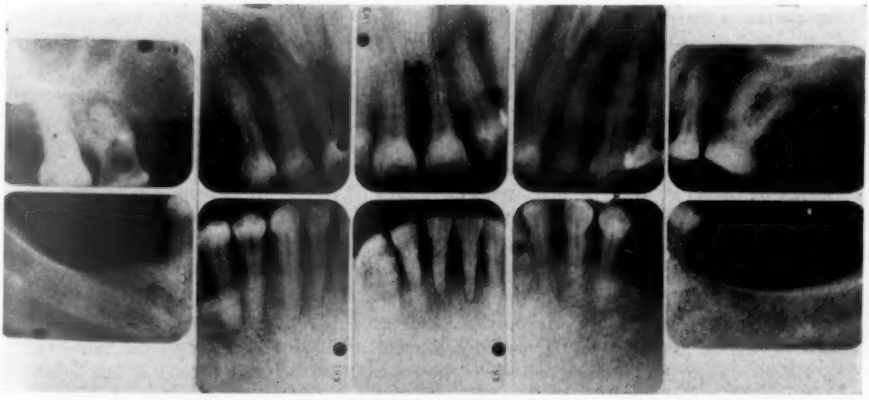


Fig. 1.—Case 1. Intraoral roentgenograms. Note the severe carious destruction of the crown of the upper left second molar and the resulting apical rarefaction. There is also a considerable degree of generalized alveolar bone loss.

and intraoral roentgenograms revealed extensive carious involvement, with pulpal exposure of the upper left second molar, as shown in Fig. 1. The upper left third molar was also carious. The gingivae surrounding these teeth were inflamed and edematous, and there were deep pockets from which pus could be expelled by digital pressure. As seen in Fig. 1, periapical radiolucencies and marked resorption of alveolar bone were also present. Clinical and roentgenographic examinations, therefore, revealed the following:

1. Caries of upper left second and third molars with pulp exposure of second molar.
2. Periapical osteitis.
3. Marked alveolar bone resorption.
4. Chronic gingival inflammation with pus formation.

Following consultation with the patient's physician, it was decided that the upper left second and third molars should be extracted. The dietitian was asked to prepare the diet in liquid form, without altering its nutrient composition. This was done by means of a Waring Blendor. On the following day the patient was brought to the dental clinic, where both teeth were extracted under local procaine anesthesia. The extractions were uncomplicated and the wounds were permitted to drain freely. Curettage was not attempted, and no drugs, antibiotics, or chemotherapeutic agents were administered. Bleeding was easily controlled by biting pressure on gauze pads. Beginning with the twelfth postextraction hour, warm saline mouth rinses were prescribed at three-hour intervals. On the following day, the patient was seen and the wound was inspected. On the next day, a triangular spicule of bone, approximately 1 mm. wide at its base and 2 mm. in length, was noted emerging through the gingiva close to the palatal edge of the wound. It was loose and easily removed with a forceps. The wound drained and healed without further incident. The only change in the patient's study during this time was the substitution of a liquid diet of unaltered composition for the regular solid diet. This was begun on the day prior to the extraction and continued for two days thereafter.

Data: The effects of the infectious and inflammatory processes and the related oral surgical procedures upon the patient's protein metabolism are summarized in Fig. 2, in which nitrogen balance is plotted versus time. The Roman numerals in Fig. 2 refer to three-day metabolic periods. During period I, a negative balance of approximately -3 grams of nitrogen per day existed. During period II, the balance fell to -6 grams of nitrogen per day. With onset of period III, nitrogen loss was stabilized. A trend toward a more positive balance began during period IV. On the eleventh day, during period IV, the extractions were performed. During period V, the patient exhibited the same trend toward a more positive balance (that is, decreased nitrogen loss) as was seen in period IV. During period VI, however, a subsequent marked *increase* in nitrogen loss occurred. Since it is usual for adjustments in nitrogen excretion to exhibit a lag period of several days prior to becoming evident in the balance data,[1] it is likely that the stresses of the extraction procedure and of the underlying infection and inflammation resulted in this marked increase in nitrogen loss. The patient was losing -9.4 grams of nitrogen per day during metabolic period VI. Recovery from this sharp increase in nitrogen loss was manifested in period VII.

Comments: The foregoing data are of interest for several reasons. We note first that, although the patient was subjectively asymptomatic at the beginning of the study, she was even at that time (periods I, II, and III) in slight negative balance, probably as a result of active oral infection and inflammation. Next, let us consider the trend toward a more positive balance exhibited during the third through the fifth metabolic periods. This might have been due to spontaneous subsidence in intensity of the infectious and inflammatory processes. However, two additional factors may have been involved here. First, the metabolic data indicate that this patient was probably experiencing episodes of negative nitrogen balance for some time prior to study on the ward. In an organism in negative nitrogen

balance over a period of time, nitrogen loss tends to *decrease*. This is a reflection of the fact that a protein-depleted organism utilizes and conserves nitrogen more efficiently than one in nitrogen equilibrium or in positive balance.[29] Second, as an organism is subjected to the effects of continued negative nitrogen balance, its available tissue proteins are depleted and hence its tissue nitrogen sources decline.[29] Since less tissue nitrogen is available, nitrogen loss is decreased. An idea of the magnitude of tissue loss represented by 9.4 grams of nitrogen (period VI) may be gained from application of a conversion factor taken from the work of Reifenstein, Albright, and Wells,[1] who calculated that 1 gram of excreted nitrogen represents 32 grams of muscle in vivo; thus, 9.4 grams of nitrogen = 9.4 × 32 = 300 grams = ⅔ lb. of muscle lost per day.

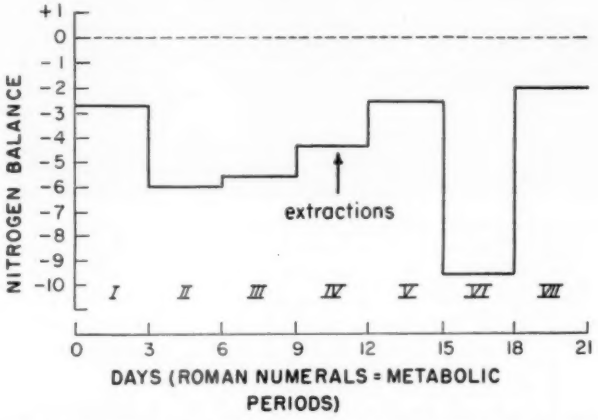


Fig. 2.—Case 1. Nitrogen balance data. Note that the patient was in negative nitrogen balance when the study began. At the time that the extractions of the upper left second and third molars were performed, a trend toward decreasing nitrogen loss had been established. The metabolic response to the extractions was a marked increase in nitrogen loss, as may be seen in period VI. The significance of the catabolic response following trauma (deliberate or accidental) is not fully known.[66]

The importance of oral health to the well-being of the patient with diabetes mellitus, a relationship recognized and appreciated by all physicians and dentists, is re-emphasized in the foregoing data. The catabolic effects of oral infection, inflammation, and surgical stresses upon the metabolism of the patient with uncontrolled or poorly controlled diabetes mellitus are demonstrated dramatically in the nitrogen loss exhibited by this patient. It will be instructive to compare this study with that of Patient J. G. (Case 2), who also had diabetes mellitus, and with that of Patient R. C. (Case 3), who was not diabetic but who experienced multiple dental extractions and an alveoloplasty during his balance study.

CASE 2 (PATIENT J. G., M.S.H. #39-6297).—

Case summary: This 64-year-old white man was also admitted to the Metabolism Research Ward of the Mount Sinai Hospital for study of factors responsible for poor control of his diabetes mellitus. He had been treated in the outpatient diabetes clinic for a nine-year period, when it was noted that his diabetes was becoming increasingly difficult to manage. Since the patient was edentulous and wore well-constructed, efficiently functioning acrylic dentures, it was felt that observation of his oral tissues during controlled shifts in metabolism would provide an interesting comparison to the previous case. Examination of the patient's oral tissues showed that the lips, tongue, oral mucosa, gingivae, and floor of the mouth exihibited no signs of pathology. Intraoral roentgenograms (Fig. 3) showed a bone pattern typical of an edentulous mouth and free from evidences of pathology. This

patient remained on the ward for forty days, during which time his insulin requirements were studied. His metabolic responses to various levels of insulin intake are described below, together with observations on his oral tissues.

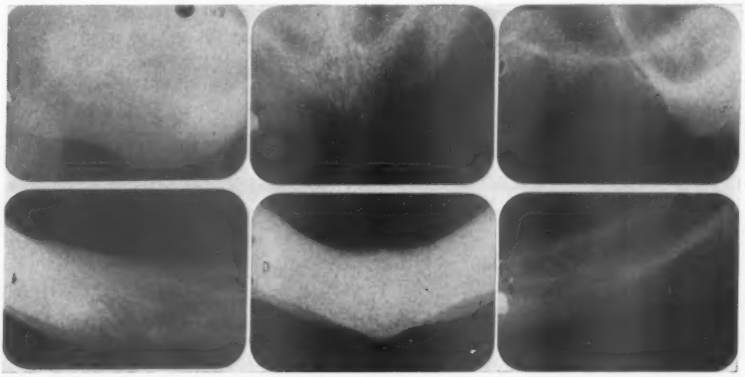


Fig. 3.—Case 2. Intraoral roentgenograms. The appearance of the maxilla and mandible is typical of an edentulous mouth. There were no signs of oral pathology, roentgenographically or clinically.

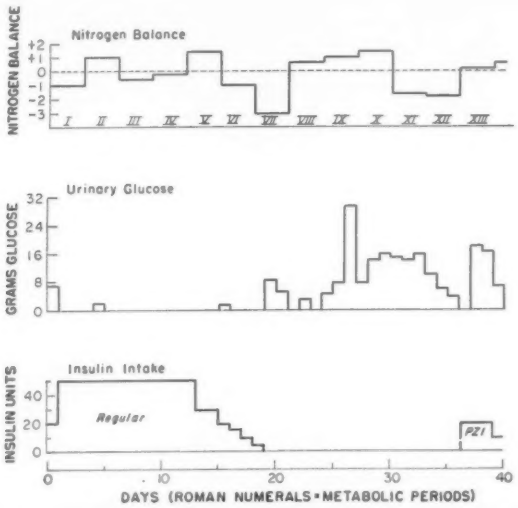


Fig. 4.—Case 2. Metabolic data. From bottom to top are plotted insulin intake, urinary glucose excretion, and nitrogen balance data. Note that urinary glucose excretion and insulin intake are inversely correlated. The patient was in nitrogen equilibrium during most of the study and in negative balance only during insulin withdrawal. No clinical oral tissue changes were detectable during the metabolic shifts represented above.

Data: In Fig. 4 are plotted, from bottom to top, insulin intake, urinary glucose excretion, and nitrogen balance during the course of this study. For the first twelve days (except for the first day) the patient was maintained on 50 units of regular (crystalline) insulin per day. During this time, his urine was essentially sugar-free, and he was in nitrogen equilibrium (that is, balance was between +1.5 and -1.5 Gm. per day). Beginning with the thirteenth day, insulin intake was lowered in stepwise fashion until on the nineteenth day it

was zero. As insulin intake was lowered, the appearance of glucosuria was noted. Coincident with insulin withdrawal and the appearance of glucosuria was the occurrence of a slight negative nitrogen balance. The extent of nitrogen loss was approximately -3 grams nitrogen per day as seen in period VII. As insulin continued to be withheld from the patient, the extent of glucosuria increased markedly. The nitrogen balance recovered from its slight negativity, however, and the patient was again in nitrogen equilibrium. At no time during these metabolic shifts were any significant clinical changes noted in the oral tissues, although the patient was seen at least once each day. On the thirty-seventh day of the study, daily administration of 15 units of protamine zinc insulin was begun. This was accompanied by a brief rise in urinary glucose output, which quickly subsided. Nitrogen equilibrium was evident during the latter phases of study. It is important to note that at no time during the occurrence of the above-described glucosuria did the patient become ketotic.

Comments: Clinical changes in oral tissue were not seen in this patient in response to the induced metabolic fluctuations. It must be noted, however, that the nitrogen shifts produced in this instance were relatively mild in comparison with the changes observed in Case 1. In considering these differences, we must not lose sight of the possible influence of factors associated with the presence of diseased teeth and supporting structures, which were present in Case 1 but not in Case 2. Dental and periodontal factors which might increase the metabolic demands of the oral tissues and which might provide favorable sites for infection and inflammation were obviously not operative in Case 2. One can only speculate as to whether or not results would have been the same had severe caries or periodontal infection been present in this man. Other data obtained during the study revealed that Patient J. G. could be controlled by diet regulation alone and that his insulin intake could be completely eliminated. It was impossible to induce ketosis on a daily intake of 150 Gm. carbohydrate, 100 Gm. protein, 100 Gm. fat, and *no insulin*. Compared to Patient S. S. in Case 1, this patient was considered to have a milder form of diabetes mellitus.

CASE 3 (PATIENT R. C., B.V.A.H. #53788).—

Case summary: A 60-year-old white man was admitted to the Veterans Administration Hospital on Jan. 24, 1956, with a complaint of pain in the left thigh and lower back. Physical examination was essentially negative, as were hemograms and serum determinations for calcium, phosphorus, albumin, globulin, acid and alkaline phosphatases, and cholesterol. Roentgenograms revealed resorption of bone affecting the vertebrae, ribs, maxilla, and mandible, as well as numerous calculi in the gall bladder. Bence Jones protein was absent from the urine, and bone marrow smears were also negative for multiple myeloma. Urinary steroid and amino acid excretions were normal. Glycosuria was present (1+ to 2+), although blood sugar values and glucose tolerance curves showed no abnormalities. The following conditions were eliminated as *detectable* causes of the bone resorption: hyperparathyroidism, cancer, osteomalacia, multiple myeloma, disturbances in acid-base balance, and senile osteoporosis. The condition progressed with decrease in x-ray density and compression of vertebrae T12, L2, L3, L4 and L5 (Fig. 5). There was also evidence of spontaneous fractures involving ribs 7 and 10 on the right side.

Dental history revealed that the patient had experienced a left parotid gland infection twenty-five years previously. Nothing further of importance was noted until approximately three years prior to admission, when he noted a loss of acuity of taste and smell. One and one-half years later the upper central incisors had become so loose that he said he could almost remove them with his fingers.

Examination of the oral cavity revealed that the tongue, the lips, the oral mucosa, and the floor of the mouth showed no pathology. The gingivae were somewhat edematous with chronic inflammatory changes. There were generalized calculus and pocket formation; teeth were quite mobile. Intraoral roentgenograms are shown in Fig. 6.

The etiology of this condition is not known; nor has a diagnosis been made. The patient was admitted to the Metabolism Research Ward for study of nitrogen, calcium, and

phosphorus metabolism. During his stay on the ward, because of difficulty in mastication and in order to prepare the mouth for dentures, extraction of the remaining teeth, and alveoloplasty were performed in one operation. The following teeth were extracted:

$$\frac{8,7,3,2 \mid 2,3,5}{5,4,3,2,1 \mid 1,2,3,4,5,7}$$

Since the patient was under study at this time, it was possible to follow his nitrogen balance prior to, during, and following these extensive oral surgical procedures.

Fig. 5.—Case 3. Roentgenogram of vertebral column. The uppermost vertebral body is T_{12}; below it is L_1. The appearance of L_1 is typical of the nondiseased state (rectangular in outline, the opposite sides being roughly parallel). Note that T_{12} is wedge-shaped and that its lower border cups inwardly. Note also that L_2, L_3, and L_4, also shown on the film, depart from the normal rectangular shape. In each of these, the dorsal and ventral vertebral surfaces cup inwardly, and the rectangular shape of the body is distorted.

The purpose of these studies was (1) to determine whether or not the skeletal disturbances, including the alveolar bone resorptions, were in any way associated with metabolic balance abnormalities and (2) to determine whether the extensive oral surgical procedures would be sufficient stress to induce a catabolic response in the patient.

Data: Nitrogen balances were obtained during four three-day metabolic periods. Two periods preceded and two periods followed the oral surgical procedures. Data relating to calcium and phosphorus metabolism are based upon dietary intake and urinary excretions; fecal calcium and phosphorus determinations were not made in this study.

Nitrogen balance: In Fig. 7 are shown the nitrogen balance data. During periods I and II, which served to establish a control prior to extractions and alveoloplasty, the patient exhibited a negative nitrogen balance of -5.02 and -5.31 Gm. per day, respectively. On the first day of period III, extraction of the patient's remaining eighteen teeth and alveoloplasty were performed. During the

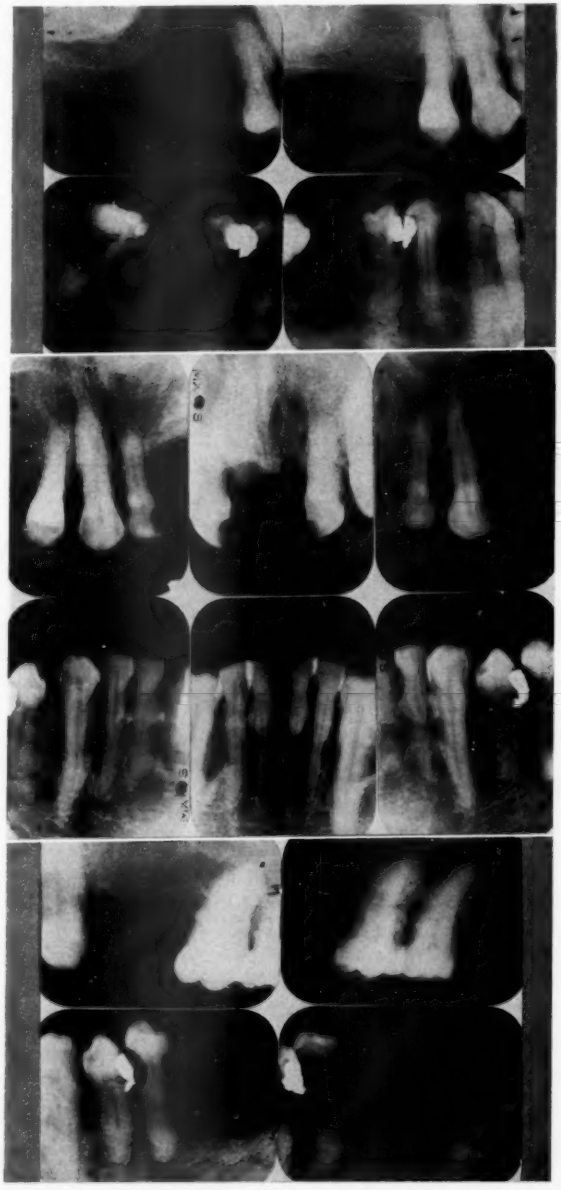


Fig. 6.—Case 3. Intraoral roentgenograms. Generalized alveolar bone resorption is evident, as are caries and heavy calculus deposits. From the patient's history, it was not until approximately three years prior to these films that loosening of the upper incisors occurred. This was followed by a rapid deterioration of the periodontal structures, increased caries experience, and accumulations of calculus such as are shown on the films.

postoperative periods III and IV, the nitrogen balance remained essentially unchanged from the control periods. It thus appeared that in this patient, in contrast to the patient in Case 1, multiple extractions and alveoloplasty did not result in increased nitrogen loss during the periods studied. This may have been due to the possibility that tissue nitrogen stores were depleted or that in this patient the stress of multiple extractions and alveoloplasty was insufficient to call forth an increased catabolic response.

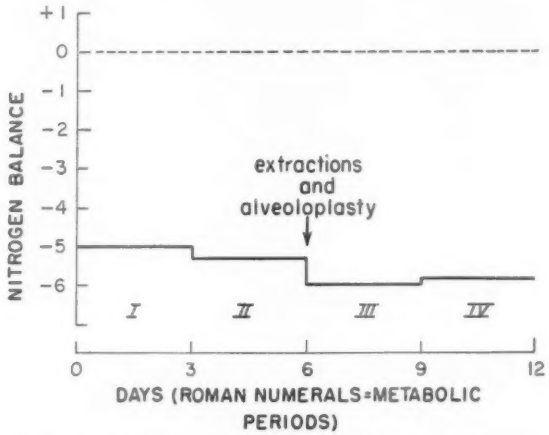


Fig. 7.—Case 3. Nitrogen balance data. This patient was in negative balance during the entire study (and probably prior to the study, as well). It is interesting to note that multiple extractions and an alveoloplasty were not associated with an increased nitrogen catabolism, in contrast to the response noted in Patient S. S., Case 1 (diabetes mellitus), in whom a simpler surgical procedure was associated with a marked catabolic response.

Calcium and phosphorus metabolism: Although *total* balance studies relating to these elements were not possible, two procedures were used to investigate their metabolism. In the first, urinary calcium and phosphorus excretions were followed while the patient was on a low-calcium (Bauer-Aub type) diet. In this procedure, on a daily intake of approximately 100 mg. calcium, urinary excretion of 150 mg. calcium represents a questionable negative balance, while daily urinary excretion of 200 mg. or more is generally considered to reflect a negative calcium balance.[31]

The second procedure was a "calcium-load test," designed to elicit data concerning calcium-phosphorus and parathyroid-renal interactions.[32] In this procedure 10 to 20 mg. calcium per kilogram of body weight are infused intravenously (as the gluconate) over a four-hour period. The usual response to such an infusion is a drop in urinary phosphorus excretion on the day of the infusion. (A possible mechanism for the lowered urinary phosphorus excretion in response to calcium infusion might be the depression of parathyroid hormone formation by elevated serum calcium levels resulting from the infusion. This, in turn, tends to increase renal tubular phosphate reabsorption, leading to a drop in urinary phosphate excretion.)

The above procedures are not as quantitative as total balance determinations, and there is some disagreement as to their exact physiologic meanings. However, each is capable of yielding valuable semiquantitative data which reflect the metabolism of calcium and phosphorus. The first such tests were performed in March, 1956, while the patient's daily intake of calcium was 103 mg. In Table II the urinary calcium and phosphorus excretions in milligrams per day are shown, together with the results of a "calcium-load" test performed during the latter part of the study.

It may be seen from Table II that during the first ten days of the study, and prior to the calcium infusion, there was a questionable negative calcium balance on four days (excretions: 163, 180, 147, and 174 mg.) and a definite negative balance on six days (excretions: 478, 205, 220, 229, 212, and 201 mg.). These data establish that the patient was losing more calcium from his body than he was ingesting in his food. The excess calcium was derived, presumably, from the skeleton.

Turning now to the "calcium-load" test, it will be noted in the lower portion of Table II that the urinary phosphorus excretion on March 12 (representing the collection of the day of the calcium infusion) was not appreciably lowered from that of the previous day. This would indicate an abnormal response to the calcium infusion.

TABLE II. URINARY CALCIUM AND PHOSPHORUS EXCRETION (MG./DAY) ON A DAILY INTAKE OF 103 MG. CALCIUM

DATE	CALCIUM	PHOSPHORUS
3/2/56	163	491
3/3	478	1040
3/4	180	468
3/5	205	553
3/6	220	562
3/7	229	497
3/8	212	548
3/9	147	560
3/10	201	603
3/11	174	475
	Infusion of 20 mg. calcium per kilogram on 3/12/56	
3/12	920	454
3/13	124	394
3/14	174	612
3/15	177	398

It is of interest to note that both these procedures (determination of urinary calcium excretion on a low-calcium intake and the "calcium-load" test) were repeated in June, 1956 (approximately three months later), and that on this later date results in both tests were normal. The urinary calcium excretion was less than 100 mg. per day on the low intake, and urinary phosphorus was *significantly depressed* by the same intravenous calcium-load procedure.

Additional tests of renal function were performed for this patient. These included determinations of phosphate reabsorption,[33] creatinine clearance,[34] and phenolsulfonphthalein excretion.[35] The phosphate reabsorption and creatinine clearance determinations gave values which were in the range of low normal (that is, 82 to 86 per cent phosphate reabsorption and 86 to 106 c.c. per minute creatinine clearance). Phenolsulfonphthalein excretions, however, were consistently *below* normal—26 per cent excreted in one hour and 15 per cent excreted in one hour, on separate occasions (normal excretions, 40 to 60 per cent in one hour).

Study of sections of gingiva and bone removed during the extractions and alveoloplasty procedure revealed no histopathology in these tissues. A subsequent iliac crest biopsy was also negative.

Comments: This case presents a variety of challenges. Unfortunately, it has been impossible to arrive at a definitive diagnosis of the disease process or processes. The generalized metabolic disturbances (negative nitrogen balance, impaired renal function, glycosuria in the absence of hyperglycemia, or abnormal glucose tolerance) apparently first manifested themselves as loss of bone and loosening of the upper incisors. Of great interest to the dentist, of course, is the fact that in this patient we find the coexistence of alveolar bone resorption (as part of a generalized skeletal involvement), negative nitrogen balance, intermittent negative calcium balance, and disturbances in renal physiology. Against such a background, the lack of effect which the extraction of eighteen teeth and alveoloplasty had upon the patient's nitrogen balance stands in marked contrast to the experience in Case 1.

In Case 1, the patient, who was diabetic, only two teeth were extracted in a much less involved surgical procedure, with a resulting profound increase in nitrogen catabolism. In addition to the possible reasons already offered for this discrepancy, we must also recall that acute infection and inflammation were present in the diabetic patient and not in the patient in Case 3. This divergence in metabolic response points to the necessity for intensive investigations of conditions during which surgery and other manipulations within the mouth may induce metabolic derangements of significance for the welfare of the patient.

CASE 4 (PATIENT S. S., B.V.A.H. #62030).—

Case summary: This 41-year-old white man of Sicilian birth was admitted to the Veterans Administration Hospital on Dec. 11, 1956, with a complaint of bleeding and receding gingivae. He said that three months prior to admission his right maxillary second molar was extracted because of caries and that two weeks later the "blood clot" broke down and blood and coagulated material came out of the socket. He returned to the dentist and was treated with penicillin lozenges. Swelling, inflammation, and pain continued to develop in the posterior quadrants of the mouth. He visited another dentist who recommended extraction of both lower third molars. This was done, but the patient experienced the same symptoms. He claimed to have hemorrhaged and to have removed "cakes" of blood and tissue from his gingivae. His dentist recommended that, because of the nature of his complaints, he see a physician. He also informed the patient that severe alveolar bone resorption and gingival recession were occurring. The patient's physician found traces of blood in his stool and also reported him to be anemic. The patient was then admitted to this hospital.

Physical examination was essentially negative. Acid and alkaline phosphatase, serum calcium and phosphorus, bleeding time, and coagulation time were all within average ranges of values. Urinalysis was negative. No Bence Jones protein was found, and bone marrow smears for multiple myeloma were negative. Tests for C-reactive protein (to disclose possible masked infection or inflammation[36]) were also negative. Serum glutamic-oxaloacetic transaminase determination[37] revealed no abnormalities. Serum electrophoresis[38] disclosed a normal spectrum of serum proteins. A roentgenographic skeletal survey disclosed no abnormalities of the skull, vertebrae, long bones, or pelvis.

The hemogram was: red blood cells, 3,480,000; hemoglobin, 11.7 grams; white blood cells, 4,150; neutrophils, 60 per cent; lymphocytes, 39 per cent; monocytes, 0; eosinophils, 1 per cent; basophils, 0; sedimentation rate, 6 mm.; hematocrit value, 39 per cent. This was considered to be consistent with an anemia resulting from excessive blood loss.

Oral examination revealed no pathology of tongue, lips, or mucous membranes. There was marked gingival recession about the molars in all four quadrants (Figs. 8 and 9). The degree of gingival recession decreased anteriorly, the cuspids were also affected, and the incisors not at all. The gingival margins in the molar regions were rolled and appeared detached or pushed away from the teeth; they were slightly edematous. There was very little redness or acute inflammatory change, even in areas of severe recession. In fact, there was a striking *lack* of inflammatory phenomena associated with the gingival recession. The root surfaces of the molars were exposed to a depth of approximately 5 to 6 mm. The exposed surfaces were clean and smooth and appeared almost as highly polished as enamel. There was very little, if any, calculus, either supra- or subgingivally. This was not the result of professional treatment, for as gingival recession occurred the exposed root surface appeared smooth, glossy, and free of calculus and debris. It is possible that the patient may have cleansed the root surfaces himself, although their high luster and polish speak against this.

This patient worked as a paint sprayer of display cards but said that he did not use lead paints and that he had never been excessively exposed to them. His mother had diabetes mellitus. Because of the lack of physical and chemical findings, the patient was admitted to the Metabolism Research Ward for study of nitrogen, calcium, and phosphorus metabolism. His study lasted for twelve days, nine of which were devoted to total balance determinations.

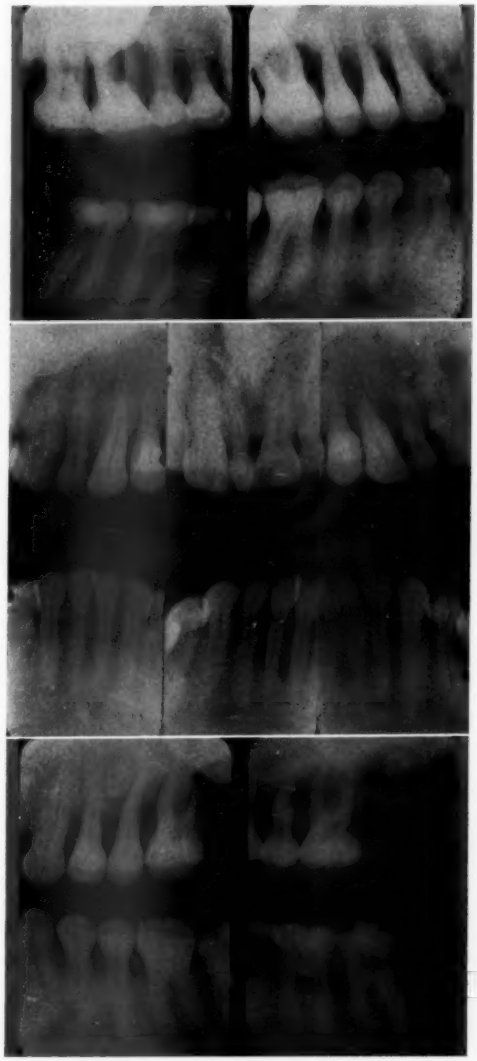


Fig. 8.—Case 4. Intraoral roentgenograms. There is considerable loss of alveolar bone in all the molar areas. The amount of loss decreases anteriorly. The incisors are not significantly affected, but the peg-shaped supernumerary tooth between the upper central incisors has experienced some loss of its supporting alveolar bone.

Data:

Nitrogen balance: The nitrogen balances for the three metabolic periods were -1.16 Gm. per day, -0.57 Gm. per day, and -1.01 Gm. per day, all of which represent equilibrium values.

Calcium and phosphorus balances: Calcium balances were also within normal limits. On a daily intake of 150 mg. calcium, urinary excretions varied between 72 and 85 mg. per day. Total balance determinations revealed slight negative balances ranging between -36 and -62 mg. per day. These figures are considered to represent equilibrium values.

Fig. 9.—Case 4. Photograph of mouth illustrating exposure of the roots of the posterior teeth, especially the upper ones. Note the lack of calculus and inflammatory response. The root surfaces were remarkably clean, very smooth, and almost as highly polished as enamel.

Only in the case of phosphorus were there obtained balances which might be considered to represent real losses. Thus, during periods I, II, and III, the phosphorus balances were -222 mg. per day, -60 mg. per day, and -213 mg. per day, respectively. It is felt that while -60 mg. per day might represent an equilibrium value, the two other balances are definitely negative. Study of the analytic data revealed no reasons for suspecting that errors in technique may have been responsible. Creatinine excretions were determined to check on adequacy of urine collections, and these also were in order. We are thus faced with what appears to be negative phosphorus balances, with normal serum phosphorus levels and coexisting nitrogen and calcium equilibrium states.

A "calcium-load" test was performed, to which the response was normal (that is, depression of phosphate excretion by intravenous calcium infusion). The calcium infusion in this instance was performed according to the method of Nordin and Fraser,[39] and the data were used for calculations of urinary excretion of calcium (for recognition of osteomalacia) and for skeletal retention of calcium (for recognition of osteoporosis) in accordance with the principles outlined by these authors. No abnormalities were found.

Comments: This case is perhaps a classic example of so-called periodontosis (considering periodontosis as a descriptive term and not as a distinct clinical entity). It is remarkable that such rapid alveolar bone loss occurs in the absence of detectable abnormalities. This lack of detectable abnormalities is perhaps overstressed, but the absence of inflammatory phenomena inevitably leads one to suspect that a metabolic defect of some sort exists in these patients. The only possible metabolic abnormality detected in this patient was that reflected in the negative phosphorus balances. Interpretation of the phosphorus loss eludes us, however, and since only one patient is involved, additional studies are needed in order to establish the meaningfulness of the observation.

CASE 5 (PATIENT S. M. K., B.V.A.H. #64300).—

Case summary: A 29-year-old Negro man was admitted to the hospital because of poor vision resulting from bilateral cataracts of two years' duration. While on the eye service, hypocalcemia and hyperphosphatemia were noted and the patient was transferred to the Metabolism Research Ward for investigation of possible hypoparathyroidism.

The patient had entered the army on Feb. 21, 1950, and was hospitalized on Nov. 3, 1951, after having had four episodes of unconsciousness. These began with leg and arm cramps that lasted for hours, and just prior to unconsciousness dizziness was experienced. During this first hospitalization, the patient had a grand mal seizure on Dec. 5, 1951, and was placed on Dilantin therapy. Phenobarbital was added to this on Jan. 10, 1952. Because of developing paranoid behavior attributed at that time to possible Dilantin toxicity, medication was changed to Mesantoin. A serum calcium determination on Nov. 13, 1951, was normal. The patient experienced amnesia of seizures.

The patient was discharged from service in October, 1952, and there was no documented seizure from that time until the present hospitalization. However, because of the patient's amnesia of seizures, there may not have been some unreported attacks during this period. He did have frequent episodes of peculiar feeling during which his arms and legs "drew up." The only other pertinent item in his history was a positive serologic test for syphilis in September, 1951. He was treated with 5.7 million units of penicillin. Subsequent serologic tests for syphilis have been negative.

When the patient was admitted to the Brooklyn Veterans Administration Hospital, the physical findings were negative, with the exception of an asymptomatic varicocele of the left testis. Prior to study on the Metabolism Research Ward, the blood calcium ranged between 5.9 and 6.5 mg. per cent, and blood phosphorus values were between 6.1 and 6.9 mg. per cent. Alkaline phosphatase values were normal. The blood chemistries, cataracts, and epileptic seizures indicated that the patient was hypoparathyroid, and he was transferred to the Metabolism Research Ward for study.

Dental examination revealed a mouth in very poor condition. The cemental gingivae and oral mucosa were pale, but the marginal gingivae were edematous and inflamed. There were several carious pulp exposures, and only a shell of broken-down enamel remained of the crown of the lower right first premolar. Materia alba and calculus were present throughout the mouth. The tongue, floor of the mouth, and oral mucosa were free of pathology.

Intraoral roentgenograms (Fig. 10) revealed an interesting appearance of the alveolar bone, which was extremely roentgenopaque and granular. The bone appeared to be very dense and well calcified—excessively so, perhaps. The marrow spaces were encroached upon to a considerable extent as a result of the diffuse granular thickening of trabeculae, and the usual contrast between trabeculae and marrow spaces was eliminated to a considerable extent. Extraoral, lateral roentgenograms also revealed a dense granular appearance of the skull and mandible. In the lateral films, the granularity suggested a *peau d'orange* effect (Fig. 11).

The patient was placed on the Metabolism Research Ward for study of nitrogen, calcium, and phosphorus metabolism. The study lasted for ninety days, during which time the patient was treated with vitamin D_2 (calciferol), A.T. 10 (dihydrotachysterol), and parathyroid extract.

Data:

Nitrogen balance: The patient's nitrogen balance was determined for nine three-day periods from May 8 to June 4, 1957. During this time, he was in equilibrium and at no time departed from the equilibrium state.

Calcium and phosphorus metabolism: At the beginning of the study, the patient's serum calcium was 7.9 mg. per cent and his serum phosphorus was 6.4 mg. per cent. The urine was essentially calcium free, as is most often the case in hypoparathyroidism. In Fig. 12 data of the study between periods IX and XIX are shown. The medications used appear above; below this are depicted serum calcium and phosphorus values. To the right are urinary calcium excretions. Phosphorus excretion is shown in the lowermost set of curves.

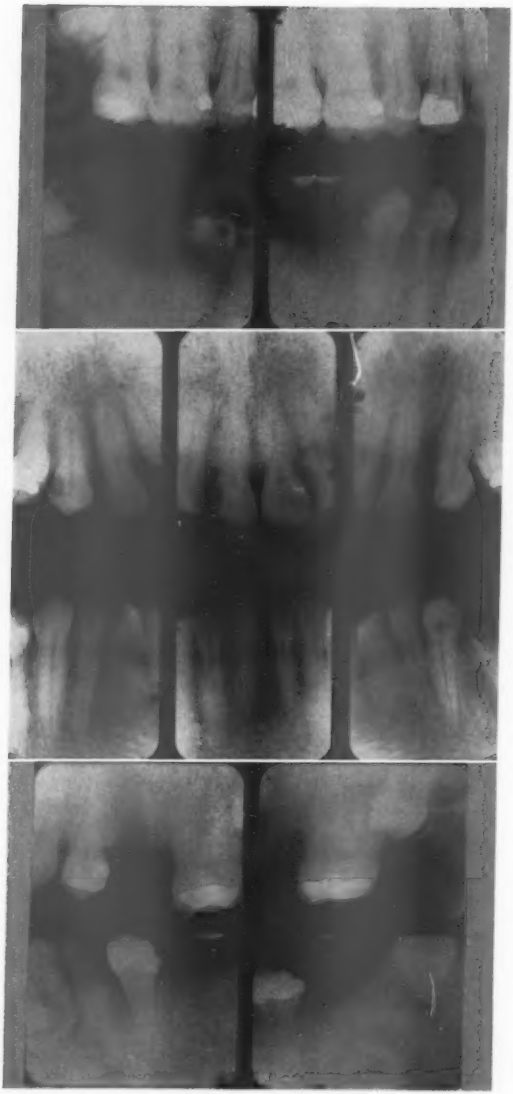


Fig. 10.—Case 5. Intraoral roentgenograms illustrating the roentgenopaque qualities of alveolar bone. Note in the molar areas particularly that the usual contrast between trabeculae and marrow spaces is lessened considerably. Note also that the lower molar areas (which in the adult remain actively hematopoietic and often are most translucent to x-rays) are especially opaque.

Fig. 11.—Case 5. Lateral jaw roentgenogram illustrating the dense bone formation. Note the *peau d'orange* effect in the bone overlying the upper molar roots.

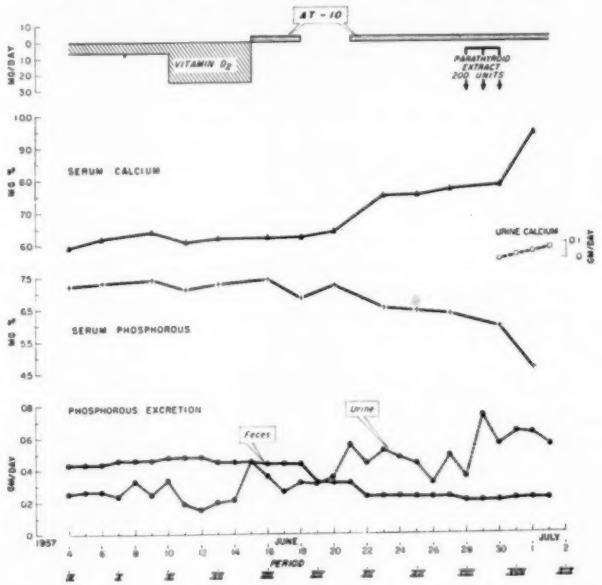


Fig. 12.—Case 5. Metabolic data. Summary of serum calcium and phosphorus levels, and calcium and phosphorus excretion during therapy (supervised by Dr. D. Robert Axelrod, Chief, Metabolism Research Ward). The data begin with period IV; the levels shown at that time reflect levels during periods I to III which are omitted for reasons of space.

Because it was not until the study was well under way that treatment produced results, the early periods of study are not shown in Fig. 12. However, control values were established prior to treatment (periods I to IV); their levels were maintained and are shown in the values of the curves that appear during the first few periods shown in Fig. 12. Treatment was begun in period V, with the administration of 6.25 mg. per day of vitamin D_2. This was without effect, as was an increased dose of 25 mg. per day (Fig. 12). Vitamin D_2 was administered until the end of period XIII, when A.T. 10 was started. It will be seen that administration of 4.75 mg. per day of A.T. 10 immediately set in motion the desired therapeutic effects, namely, a lowering of serum phosphorus and a somewhat less rapid elevation of serum calcium. The urine was still calcium-free, however. A.T. 10 administration was continued (with a lapse of three days) until period XIX. It may be seen that between periods XIII and XVI a dramatic rearrangement of metabolic processes occurred. During this time serum calcium values rose from 6.2 to 7.5 mg. per cent, and serum phosphorus declined from 7.3 to 6.4 mg. per cent. The excretory pattern for phosphorus also was re-established along normal lines, that is, the major excretory path was now via urine. Urinary calcium, however, was still not detectable. The re-arrangements described above continued and were intensified by the administration of 200 units per day of parathyroid extract, during period XVIII, as shown in the upper right-hand portion of Fig. 12. It may be seen from the curves that by period XIX calcium had risen to 9.4 mg. per cent and phosphorus had declined to 4.6 mg. per cent. It was not until after administration of parathyroid extract that calcium was detected in the urine. As more normal serum and excretory levels were established, the clinical condition of the patient improved considerably. Concomitant changes in alveolar bone were not detectable. The patient was seen after having been on effective therapy for three months, and intraoral roentgenograms taken at the end of this time revealed little change from those taken at the beginning of the study.

Comments: The intraoral and extraoral roentgenograms in this case will be considered first. Although an increase in bone density might be expected in hypoparathyroidism, as Albright and Reifenstein[40] point out, this is not always found. The increase in roentgenopacity of the alveolar bone of this patient demonstrates in unmistakable fashion the nature of the expected change. It has also been known, since Erdheim's first demonstration in the rat incisor,[41] that hypoparathyroidism occurring during tooth calcification results in acalcification. This has also been shown in human beings by Albright and Strock,[42] who demonstrated a characteristic lack of root formation in patients in whom root development and the hypoparathyroid condition coexisted. The lack of developmental defects in the dentition of the present patient indicates that the disease process must have begun in adult life, and indeed the first symptoms were noted in 1951 when the patient was 23 years of age.

The metabolic data are classical in nature. The biochemical picture of low serum calcium, elevated serum phosphorus, normal alkaline phosphatase, and absence of calcium in the urine, taken together with the clinically evident tetany, epilepsy, and cataracts, encompass major features of the disease. The responses to therapy and the metabolic rearrangements, as reflected in calcium and phosphorus shifts in blood and excreta, are well demonstrated in Fig. 12 and require no further emphasis at this time.

This case also reminds us that the patterns of alveolar bone trabeculae respond not only to masticatory stresses and strains but also to metabolic factors. That trabecular bone is involved in regulation of the calcium levels of tissues and fluids of the body (the milieu interne) was stressed by Bauer, Aub, and Albright[43] in 1929. There is accumulating evidence that not only calcium but also sodium, potassium, and other electrolyte levels are regulated in part by reactions of trabecular bone.[44] The roentgenographically demonstrated alterations and thickening of alveolar bone trabeculae in this case demonstrate their role as reservoirs for calcium deposition and withdrawal via mechanisms not primarily related to stresses of mastication.

Although the patient had demonstrated considerable improvement in response to therapy, the fact that no roentgenographic changes were evident in the intraoral films taken after

three months of treatment is not surprising. Changes in mineral content of bone may not be detectable roentgenographically until as much as ±20 per cent of the mineral content is gained or lost.[45]

DISCUSSION

It may be said that in each of the cases studied, metabolic balance data contributed to a fuller understanding of the patient's condition and to the reaction or lack of reaction of the oral tissues, particularly alveolar bone. Thus, in the diabetic patients (Cases 1 and 2) the condition of the patient, nitrogen balance, and oral tissue reactions correlated with one another in a general fashion. Similarly, in Cases 3 and 5 (nondiagnosed generalized bone resorption and hypoparathyroidism, respectively), the condition of the patients, the metabolic data, and the alveolar bone changes also appeared to correlate well. The lack of disturbance in nitrogen balance in Case 5, although in a sense a negative finding, is nonetheless a highly significant one for an understanding of hypoparathyroid disease. The challenge presented by Case 4 is reminiscent of "periodontosis" and continues to mystify. The well-known lack of definitive alterations in body chemistry in such persons was confirmed, with the possible exception of the negative phosphorus balances encountered in this patient. Interpretation of these negative balances, however, must be postponed until it can be determined that they represent a reproducible phenomenon.

The data of this study indicate that, through balance studies, metabolic interrelations of alveolar bone and other tissues of the body might be better understood in a variety of situations in which the dentist must assume full or partial responsibility for management of the patient. Thus, the variation in response to oral surgical procedures encountered in Cases 1 and 3 calls to our attention the very great need for intensive study of the general problem of surgical and other manipulations of oral tissues and the possible production of metabolically significant stresses. In addition to tooth extraction and alveoloplasties, gingivectomies, biopsies, fractures, etc., merit study along these lines. Similarly, other problems of dental medicine, such as salivary gland diseases, oral infections, and oral tissue changes in nutritional and hormonal imbalances, might be better understood if investigated by these methods. In addition to references already listed, the summarized experiences of Cuthbertson,[46] Selye,[47] and Moore[48] provide a vast body of information and data which, by extension, support the contention that further studies along these lines are needed in dentistry. The review by Cuthbertson[46] is particularly recommended for its discussion of the significance of negative nitrogen balances under various conditions.

The data obtained in this beginning investigation indicate that carefully planned, long-term metabolic balance studies would contribute materially to our understanding of a number of important problems of dentistry. In addition, such studies would lead to a more fruitful collaboration with our medical colleagues in the study and management of cases of mutual interest.

SUMMARY

1. The organization and performance of metabolic balance studies in patients with alveolar bone disease have been described.

2. Metabolic balance data were obtained in five patients and correlated with alveolar bone reactions. Four of these patients had generalized metabolic disease; the fifth had severe alveolar bone resorption in the absence of detectable local or systemic factors that might be responsible for the bone loss.

3. With the exception of the latter patient, alveolar bone reactions and metabolic balance data correlated significantly. In the patient in whom only severe alveolar bone loss was found, a negative phosphorus balance was detected, the meaning of which is unknown at present.

APPENDIX

In this appendix we present a complete protocol of one of the studies, as well as a chart depicting the over-all features of organization of the present investigation.

A Typical Protocol

1. *Name of Patient:* S. S. *Sex:* Male *Register No.:* 62030

2. *Problem:*

Marked alveolar bone loss with inadequate local cause.

3. *Type of Study:*

Nitrogen, calcium, and phosphorus balances to be determined.
Possible calcium infusion test at beginning of fifth period.
Phosphate reabsorption test.

4. *Diet Instructions:*

Low-calcium diet (approximately 100 mg.) from Metabolism Kitchen to start 12/26/56 and continue throughout study (approximately 21 days). Aliquot of diet to be sent to laboratory for determination of nitrogen, calcium, and phosphorus content.

5. *Composition of diet:*

310 Gm. carbohydrate
53 Gm. protein
27 Gm. fat
100 mg. calcium
1,700 calories

6. *Nursing Service Instructions:*

A. 12/26/56 to 8 A.M. 1/2/57—Equilibration and orientation of patient.

B. 8 A.M., 1/2/57

(1) Start daily 24-hour urine collections (8 A.M. to 8 A.M.). Urine jars to be surrounded by ice and toluene added to urine. Twenty-four-hour urine volume to be measured, recorded, and a 200 ml. aliquot sent to laboratory.

(2) At 8 A.M., 1/2/57, patient is to receive a carmine red capsule. Stool collections are to start when carmine appears in stool. Stool periods will be three-day pools; therefore, patient will receive a marker of carmine on 1/2/57, 1/5/57, 1/8/57, 1/11/57, 1/14/57, 1/17/57, and 1/20/57. Stools between markers to be pooled and sent to laboratory.

(3) Starting 1/2/57, blood samples to be drawn on Mondays, Wednesdays, and Fridays and sent to the laboratory for calcium and phosphorus analyses. Also starting 1/2/57, blood samples to be drawn Tuesdays and Thursdays for total protein and A/G ratio determination.

C. On 1/8/57 a calcium infusion test is to be performed in the following manner:

8 A.M. Complete prior 24-hour urine collection and weigh patient. Blood sample for calcium and phosphorus. Eat breakfast.
10 A.M. Empty bladder. Record urine volume. Label and save.
10 A.M. Blood sample for calcium and phosphorus.
10 A.M. Infuse 500 ml. of 5 per cent glucose in water to which has been added 125 ml. of 10 per cent calcium gluconate. Infusion to run for four hours.
2 P.M. Infusion terminated. Draw blood for calcium and phosphorus.
2 P.M. Empty bladder. Record urine volume. Label and save.
6 P.M. Empty bladder. Record urine volume. Label and save.
10 P.M. Collect urine as at 6 P.M.

1/9/57

2 A.M. Collect urine as at 6 P.M.
8 A.M. Collect urine as at 6 P.M. Resume study as before.

1/11/57

Standard phosphate reabsorption test to be performed.

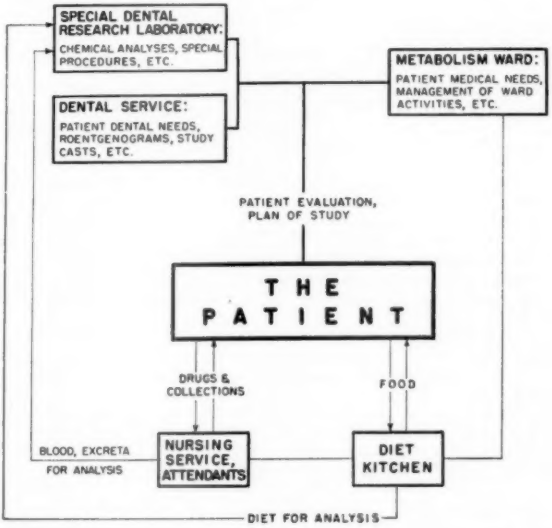


Chart 1.—The organization of metabolic balance studies of human alveolar bone disease at the Veterans Administration Hospital, Brooklyn, New York.

7. *Additional Laboratory Procedures:*

A. Serum C—reactive protein
B. Serum glutamic—oxaloacetic transaminase
C. Paper electrophoresis of serum

8. *Roentgenographic Skeletal Survey.*

9. *Dental Clinic Procedures:*

Complete dental history and examination, full series intraoral roentgenograms, study models, photographs.

The reader is also referred to Chart 1. This is a diagrammatic representation of the over-all organization of the studies performed at the Veterans Administration Hospital, Brooklyn, New York. This investigation would not have been possible without the close cooperation and willing support of all of the services shown.

The author wishes to express his deep appreciation to Dr. D. Robert Axelrod, Chief, Metabolism Research Ward, Veterans Administration Hospital, Brooklyn, New York, for making available the facilities of the ward and for many kindnesses extended during these studies, and to Drs. Herbert Pollack and John Bookman, Chief and Fellow, respectively, of the Metabolism Research Ward of the Mount Sinai Hospital, New York, at the time of the early phases of this study, for their interest and generous support. The valuable assistance of Miss Sylvia Scapa and Mr. Albert Fine, who performed the chemical analyses in this study, are also acknowledged.

REFERENCES

1. Reifenstein, E. C., Jr., Albright, F., and Wells, S. L.: The Accumulation, Interpretation, and Presentation of Data Pertaining to Metabolic Balances, Notably Those of Calcium, Phosphorus, and Nitrogen, J. Clin. Endocrinol. **5**: 367, 1945.
2. Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease, Baltimore, 1948, Williams & Wilkins Company.
3. Stein, G., and Ziskin, D. E.: The Effect of a Protein Free Diet on the Teeth and Periodontium of the Albino Rat, J. D. Res. **28**: 529, 1949.
4. Hunter, H. A.: Hypoproteinemia in Relation to the Dental Tissues, J. D. Res. **29**: 73, 1950.
5. Chawla, T. N., and Glickman, I.: Protein Deprivation and the Periodontal Structures of the Albino Rat, ORAL SURG., ORAL MED. & ORAL PATH. **4**: 578, 1951.
6. Frandsen, A. M., Becks, H., Nelson, M. M., and Evans, H. M.: The Effects of Various Levels of Dietary Protein on the Periodontal Tissues of Young Rats, J. Periodont. **24**: 135, 1953.
7. Goldman, H. M.: The Effects of Dietary Protein Deprivation and of Age on the Periodontal Tissues of the Rat and Spider Monkey, J. Periodont. **251**: 87, 1954.
8. Stahl, S. S., Sandler, H. C., and Cahn, L. R.: The Effect of Protein Deprivation Upon the Oral Tissues of the Rat, and Particularly Upon Periodontal Structures Under Irritation, ORAL SURG., ORAL MED. & ORAL PATH. **8**: 760, 1955.
9. Person, P., Wannemacher, R., and Fine, A.: The Response of Adult Rat Oral Tissues to Protein Depletion; Histological Observations and Nitrogen Analysis, J. D. Res. **37**: 292, 1958.
10. Bavetta, L. A., Bernick, S., Geiger, E., and Bergren, W.: The Effect of Tryptophane Deficiency on the Jaws of Rats, J. D. Res. **33**: 309, 1954.
11. Bavetta, L. A., and Bernick, S.: Lysine Deficiency and Dental Structures, J. Am. Dent. A. **50**: 427, 1955.
12. Stahl, S. S., Weinmann, J. P., Schour, I., and Budy, A. M.: The Effect of Estrogen on the Alveolar Bone and Teeth of Mice and Rats, Anat. Rec. **107**: 21, 1950.
13. Glickman, I., Stone, I. C., and Chawla, T. N.: The Effects of the Systemic Administration of Cortisone Upon the Periodontium of White Mice, J. Periodont. **24**: 161, 1953.
14. Nutlay, A. G., Bhasker, S. N., Weinmann, J. P., and Budy, A. M.: The Effect of Estrogen on the Gingiva and Alveolar Bone of Molars in Rats and Mice, J. D. Res. **33**: 114, 1954.
15. Glickman, I., and Shklar, G.: Modification of the Effect of Cortisone Upon Alveolar Bone by the Systemic Administration of Estrogen, J. Periodont. **25**: 231, 1954.
16. Shklar, G., and Glickman, I.: The Effect of Estrogenic Hormone on the Periodontium of White Mice, J. Periodont. **27**: 16, 1956.
17. Shroff, F. R.: Steroid Hormones and Periodontal Disease, ORAL SURG., ORAL MED. & ORAL PATH. **7**: 388, 1954.
18. Boyle, P. E.: Kronfeld's Histopathology of the Teeth and Their Surrounding Structures, ed. 4, Philadelphia, 1955, Lea & Febiger, p. 373.
19. Beube, F. E.: Periodontology, New York, 1953, The Macmillan Company, p. 450.

20. Pollack, H., Person, P., and Knishkowy, E.: Oral Lesions Seen in Diabetes Mellitus, J. Periodont. **18:** 155, 1947.
21. Swenson, H. M.: Alveolar Bone Resorption Associated With Diabetes, J. Periodont. **25:** 52, 1954.
22. Bowes, A. deP., and Church, C. F.: Food Values of Portions Commonly Used, ed. 6, Philadelphia, 1946, Anna dePlanter Bowes.
23. Ma, T. S., and Zuazaga, G.: Micro-Kjeldahl Determination of Nitrogen, Indust. & Engin. Chem. (Anal. Ed.) **14:** 280, 1942.
24. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium With a Suggested Modification, J. Biol. Chem. **63:** 461, 1925.
25. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66:** 375, 1925.
26. Kingsley, G. R.: A Rapid Method for the Separation of Serum Albumin and Globulin, J. Biol. Chem. **133:** 731, 1940.
27. Folin, O., and Wu, H.: A System of Blood Analysis, J. Biol. Chem. **38:** 98, 1919.
28. Pollack, H., and Bookman, J. J.: Riboflavin Excretion as a Function of Protein Metabolism in the Normal, Catabolic, and Diabetic Human Being, J. Lab. & Clin. Med. **38: 561,** 1951.
29. Allison, J. B.: Interpretation of Nitrogen Balance Data, Federation Proc. **10:** 676, 1951.
30. Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease, Baltimore, 1948, Williams & Wilkins Company, p. 303.
31. Bauer, W., and Aub, J. C.: Studies of Calcium and Phosphorous Metabolism. XVI, J. Clin. Invest. **20:** 295, 1941.
32. Howard, J. E., Hopkins, T. R., and Connor, T. B.: On Certain Physiologic Responses to Intravenous Injection of Calcium Salts Into Normal, Hyperparathyroid, and Hypoparathyroid Persons, J. Clin. Endocrinol. **13:** 1, 1953.
33. Chambers, E. L., and Gordan, G. S.: Phosphate Clearance in Parathyroid Disorders, J. Clin. Endocrinol. **15:** 869, 1955.
34. Everett, M. R.: Medical Biochemistry, ed. 2, New York, 1946, Paul B. Hoeber, Inc., pp. 450-454.
35. Hoffman, W. S.: Biochemistry of Clinical Medicine, Chicago, 1954, Year Book Publishers, Inc., pp. 238-248.
36. Anderson, A. C., and McCarty, M.: Determination of the C-Reactive Protein in Blood as a Measure of the Activity of the Disease Process in Acute Rheumatic Fever, Am. J. Med. **8:** 445, 1950.
37. Steinberg, D., and Ostrow, B. H.: Serum Transaminase as a Measure of Myocardial Necrosis, Proc. Soc. Exper. Biol. & Med. **89:** 31, 1955.
38. Kunckel, H., and Tiselius, A.: Electrophoresis of Proteins on Filter Paper, J. Gen. Physiol. **35:** 89, 1951.
39. Nordin, B. E. C., and Fraser, R.: A Calcium Infusion Test. I and II, Lancet **1:** 823, 826, 1956.
40. Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease, Baltimore, 1946, Williams & Wilkins Company, p. 32.
41. Erdheim, J.: Zur Kenntnis der parathyreopriven Dentin Veranderung, Frankfurt. Ztschr. f. Path. **7:** 233, 1911.
42. Albright, F., and Strock, M. S.: The Association of Acalcification of Dentine With Hypoparathyroidism in Rats and the Cure of Same With Parathormone, With Correlated Observations in Man, J. Clin. Invest. **12:** 974, 1933.
43. Bauer, W., Aub, J. C., and Albright, F.: Studies of Ca and P Metabolism: Bone Trabeculae as a Readily Available Reserve Supply of Ca, J. Exper. Med. **49:** 145, 1929.
44. Bergstrom, W.: The Skeleton as an Electrolyte Reservoir, Metabolism **5:** 433, 1956.
45. Glickman, I.: Clinical Periodontology, Philadelphia, 1953, W. B. Saunders Company, p. 552.
46. Cuthbertson, D. P.: Interrelationship of Metabolic Changes Consequent to Injury, Brit. M. Bull. **10:** 33, 1954.
47. Selye, H.: The Physiology and Pathology of Exposure to Stress, Acta Publ., Montreal, 1950.
48. Moore, F. D., and Ball, M. R.: The Metabolic Response to Surgery, Springfield, Ill., 1955, Charles C Thomas, Publisher.

ANNOUNCEMENTS

International Academy of Oral Pathology

The Academy will hold its first scientific conference in New York City on Monday, Sept. 14, 1959, at the New York Academy of Medicine.

The morning session will be devoted to an analysis of "Conditions That Predispose the Oral Mucosa to Cancer." Colonel Joseph L. Bernier of the Armed Forces Institute of Pathology will serve as moderator, with Professor Martin Rushton of Guy's Hospital in London, Professor Robert Bradlaw of the University of Durham, Newcastle-upon-Tyne; Dr. Lester R. Cahn of Columbia University, New York City, and Dr. Reidar F. Sognnaes, of Harvard University, Boston, acting as discussion leaders.

In the afternoon the subject of the conference will be "The Problem of Disturbed Odontogenesis in Relation to Tumor Formation." Dr. Lester R. Cahn will serve as moderator, with Colonel Joseph L. Bernier, Drs. Jens Jorgen Pindborg of the Royal Dental College, Copenhagen, Denmark, and Kurt H. Thoma, Professor Emeritus, Harvard University, acting as topic discussers. Drs. Harold Hillenbrand, Executive Secretary of the American Dental Association, and Henry A. Swanson, Washington, D. C., are serving as consulting associates.

Attendance at the conference will be by invitation only.

Details concerning the Charles Ulrick and Josephine Bay Lecture to be given at the New York Academy of Medicine on the same day will be announced later.

Joseph L. Bernier
Secretary-Treasurer

American Academy of Oral Roentgenology

The annual business meeting and banquet will be held on Sept. 12, 1959, at the Park Sheraton Hotel in New York City. In deference to a request from the American Dental Association that specialty groups not hold scientific sessions this year in order to cooperate more fully with the centennial program of the Association, the American Academy of Oral Roentgenology will hold no scientific session. It is hoped that as many members as possible will attend the business meeting and the banquet.

American Academy of Periodontology

The Academy will hold its annual meeting at the Barbizon Plaza Hotel, 106 Central Park South, New York City, on Sept. 10, 11, and 12, 1959.

This year's meeting will score a first in the presentation of clinical material, inasmuch as clinics will be presented from the Walter Reed Army Medical Center and the Armed Forces Institute of Pathology in Washington, D. C., and will be telecast in color with wide-screen projection in the Barbizon Plaza Hotel, New York City.

Participation in this meeting is open to all members of the American Dental Association upon the payment of a modest registration fee.

American Academy of Oral Pathology

The scientific meeting will be held on Saturday, April 18, 1959, with Charles Waldron presiding. The program follows:

Unusual Oral Syndromes. Robert J. Gorlin and Anand P. Chaudhry, Minneapolis, Minnesota.

Formation of Enamel in Ameloblastoma. Victor Kalnins, Cleveland, Ohio.

Multiple Malignant Tumors Involving the Oral Mucosa and Gastrointestinal Tract. Irving Meyer, Springfield, Massachusetts, and Gerald Shklar, Boston, Massachusetts.

The Fate of Human Follicular Sacs in Heterologous Transplantation. Martin S. Protzel, Newark, New Jersey.

Hemangioendothelioma of the Tongue. Irwin A. Small, Detroit, Michigan.

First Annual Helen McLain Lecture: The Oral Pathologist Looks at General Practice. Lester R. Cahn, New York, New York.

Symposium: Effect of High-Speed Rotary Dental Instruments on the Pulp. Joseph L. Bernier (moderator), Washington, D. C., Harold R. Stanley, Washington, D. C., Helmut A. Zander, Rochester, New York, and H. B. G. Robinson, Kansas City, Missouri.

Southern California Academy of Oral Pathology

The first annual Pacific Coast Oral Pathology Workshop is to be presented in Los Angeles on May 3, 1959. The subject of this Workshop will be "Periapical Lesions."

Approximately ten cases will be presented before a panel as a part of the program following the presentation of the papers. Any cases that Academy members have observed which could be classified as periapical lesions of typical or unusual appearance are needed for review by the Case Committee.

If members have material which they feel can be utilized by the Committee, we would appreciate receiving radiograms, clinical description, and if possible a microscopic section. The cases accepted must have sufficient histologic material for at least 100 sections.

Any questions concerning cases to be presented should be directed to Dr. David Grimm, Visiting Professor of Pathology, University of Southern California, School of Medicine, 1200 North State St., Los Angeles, California. (Phone: CApitol 5-3131, Ext. 1391.) All cases for presentation should be sent to Dr. Grimm as soon as possible.

Weldon Bullock, M.D.
Francis V. Howell, D.D.S.
Paul Hamilton, D.D.S.
Bo Wat, M.D.

American Academy of Implant Dentures

The annual meeting of the Academy will be held Sept. 11 to 13, 1959, immediately preceding the American Dental Association's centennial meeting, at the Hotel Plaza in New York City.

For information, write to Dr. A. A. Kulick, 4720 Broadway, New York, New York.

Metropolitan Conference of Hospital Dental Chiefs

All dentists on hospital staffs are cordially invited to attend a special meeting during the centennial session of the American Dental Association. The meeting will take place on Monday, Sept. 14, 1959, from 3:30 P.M. to 5:30 P.M. in the Regina Coeli Hall of St. Clare's Hospital, 427 West 52nd St., New York City.

Further particulars may be obtained from Dr. I. E. Gruber, Chairman, Special Meeting Committee, 12 Harmon St., Brooklyn 21, New York.

Internship Available at Philadelphia VA Hospital

The Veterans Administration Hospital in Philadelphia, Pennsylvania, has a one-year rotating internship available July 1, 1959. The program is given in cooperation with the affiliated dental and medical schools, and faculty members will present seminars in all specialties. The stipend is $2,500.00 per annum. A certificate of internship will be issued.

Application should be made to Dr. S. L. Orlean, Chief, Dental Service, VA Hospital, Philadelphia 4, Pennsylvania.

Michael Reese Hospital and Medical Center

A six-day course entitled "Diagnosis in Dental Practice—Procedure and Clinical Application" will be given from Monday, June 22, through Saturday, June 27, 1959. This course will be presented by the Department of Dentistry of Michael Reese Hospital and Medical Center in order to further advance the importance of diagnosis in dental practice and to emphasize the close correlation between the medical laboratory and the oral clinical and roentgenographic findings.

The faculty for the course will consist of Dr. Arthur Elfenbaum, Chief of Diagnostic Section, Michael Reese Hospital, and Professor Emeritus at University of Illinois and Northwestern Universities; Dr. Joel Glick, Diagnostic Section, Michael Reese Hospital, Assistant Professor, Northwestern University; Dr. Rachmiel Levine, Chairman, Departments of Education and Medicine; Dr. Maury Massler, Professor of Pedodontics, University of Illinois College of Dentistry; Dr. Samuel Pruzansky, Associate Professor of Orthodontics, University of Illinois; Dr. Morton Smith, Associate Director of Medical Education; and Dr. Frank Wentz, Professor and Head of Department of Periodontics, Loyola University.

The mornings will be devoted to lectures, and the afternoon periods will be devoted to clinic demonstrations and examination of patients with class participation. The fee for the course is $200.00.

The complete program and further information will be furnished on request. Write to Department of Dentistry, Michael Reese Hospital and Medical Center, 29th St. and Ellis Ave., Chicago 16, Illinois.

University of Illinois

The College of Dentistry will offer a postgraduate course on May 21 and 22, 1959, in the use of premedication in conjunction with local anesthetic agents.

The course will be directed by Dr. Elaine Stuebner, Department of Oral and Maxillofacial Surgery. The faculty will include Drs. A. G. Anderson, Head of the Department of Oral and Maxillofacial Surgery, and Bueben G. Balagot, Assistant Head of the Division of Anesthesiology. Guest lecturer will be Dr. Leonard Monheim, Head of the Department of Anesthesiology of the School of Dentistry and Associate Professor of Anesthesiology of the College of Medicine, University of Pittsburgh. Tuition for the course will be $50.00.

Another postgraduate course—endodontics for the general practitioner—will be given June 3.

This course will be under the direction of Dr. Charles G. Maurice. The faculty will include Drs. Verda E. James, Elmer A. Jasper, and Robert G. Kesel. Tuition will be $25.00.

Further information and applications may be obtained from the Division of Postgraduate Education, University of Illinois, College of Dentistry, 808 S. Wood St., Chicago 12, Illinois.

New York University

The Department of Graduate and Postgraduate Prosthodontics announces that a one-week course in the principles and practice of dental care for patients with chronic disease and disability, will be given May 18 to 22, 1959, by members of the faculty and professional staff of the New York University Dental and Medical Centers. The course is supported by the United States Office of Vocational Rehabilitation. Fifty federal scholarships are available for tuition, maintenance ($12.00 per day), and travel.

A one-week postgraduate course to familiarize practicing dentists with the latest theories of diagnosis and treatment in cleft palate prosthesis will be given May 25 through May 29 by New York University's College of Dentistry. Dr. Sidney I. Silverman is in charge of the course.

According to Dean Raymond J. Nagle: "There is considerable need for this type of postgraduate education because of the highly specialized nature of cleft palate treatment. Such treatment includes not only the correction of the physical deformity but also speech therapy."

Application forms and further information on the courses can be obtained by writing to Postgraduate Division, New York University College of Dentistry, 421 First Ave., New York 10, New York.

Tufts University School of Dental Medicine

The following postgraduate refresher courses are offered:

DPG. 908. A Special Participation Course in Full Denture Prosthesis. Monday through Friday, Sept. 21 to 25, 1959. Dr. Philip Williams, Professor of Graduate and Postgraduate Studies, and Staff. Tuition, $200.00.

(This course will be presented in English, but assistance will be available in Spanish, Italian, French, German, and Greek by competent members of the Staff.)

DPG. 908. Cosmetic Variations in Jacket Crown and Bridge Restorations Involving Periodontal Lesions. Monday and Tuesday, Sept. 21 and 22, 1959.

Dr. Charles L. Pincus, Beverly Hills, California. Tuition, $60.00.

(This course will cover the technical procedures presented in multiple jacket crown and bridge restorations.)

REVIEWS OF THE LITERATURE

MALIGNANT ORAL TUMORS

The Problem of Carcinoma of the Tongue in India. J. C. Paymaster and P. D. Shroff. Am. J. Surg. **94**: 450, September, 1957.

In 520 patients the carcinoma was located in the posterior portion of the tongue. In only 180 was the carcinoma located in the anterior portion. Of the 700 patients, 80 per cent were males and leukoplakia coexisted with carcinoma in 32 per cent. Syphilis was found in 10 per cent of the cases. In 60 per cent of cases of carcinoma of the base of the tongue there were palpable metastases in the neck, and 50 per cent of these were bilateral.

The authors are in favor of treating carcinoma of the base of the tongue with radiotherapy and report a 25 per cent five-year survival rate in the series of 520 cases. They believe that the value of surgery as a mode of therapy for a moderately advanced carcinoma of the base of the tongue is very doubtful. They recommend surgical treatment in cases of carcinoma of the anterior portion of the tongue. Of a total of 180 patients, sixty-two were treated exclusively by surgery. Hemiglossectomy was performed, followed later in many by radical neck dissection on the same side. The five-year survival rate was 32 per cent.

T. J. C.

Replantation of the Mandible in Cancer Surgery. R. L. Harding. Plast. & Reconstruct. Surg. **19**: 373, May, 1957.

A method is described for maintaining stability of the mandible and pharyngeal funnel after cancer surgery which necessitated resection of the mandible.

One method, which can be used in selected cases, is to prepare devitalized anatomic bone splint by salvaging the resected bone, cleaning out the diseased portion, and then sterilizing the residual bone in the autoclave. This splint is then fixed to the retained segments of the mandible. It has the proper shape and strength for replantation and stability, provided enough normal bone remains in the specimen to give mechanical support. The splint then seems to act as a tolerated foreign body; it becomes surrounded by a fibrous capsule and is resorbed slowly over a long period of time.

To utilize this method successfully, several prerequisites should be fulfilled. First, it should be possible to close the opening in the mouth and still have a soft tissue sleeve in which the bone spline will fit. When the patient has an epidermoid carcinoma that invades the mandible, considerable soft tissue about the primary tumor is usually sacrificed, as well as the regional lymph nodes and part of the mandible. It may not always be possible to obtain a satisfactory soft tissue closure to cover the splint in the mouth, and in such a case it is probably better to use a pin. Second, there must be enough normal bone left in the resected portion of the mandible that it can serve as a mechanical strut.

The longest period of follow-up was three years. There was resorption and nonunion, but the mandible was stable and supported a denture.

T. J. C.

A Clinical Evaluation of Malignant Melanoma. W. R. Volger, S. D. Perdue, and S. A. Wilkins, Surg. Gynec. & Obst. 106: 586, May, 1958.

From 1937 through 1956, 26,509 patients were referred to the Robert Winship Memorial Clinic at Emory University. A total of 35.6 per cent were found to have cancer. Melanoma was found in 253 patients, or 2.7 per cent of those having cancer.

One patient, or 4 per cent of those with melanoma, had the primary site in the palate.

In the treatment of malignant melanoma, surgical excision with a wide margin of normal tissue (including underlying facial structure) is advised.

Radiation plays no part in the primary treatment of malignant melanoma.

ORAL PATHOLOGY

Clinicopathological Correlations in a Series of 117 Malignant Melanomas of the Skin in Adults. N. Lane, R. Latters, and J. Molm. Cancer 11: 1025, October, 1958.

Malignant melanoma has long been considered one of the most uncontrollable neoplasms. The indications or contraindications to biopsy of a lesion suspected of being malignant melanoma prior to definitive treatment are discussed. In the authors' opinion, "Radical operations for cancer in general and for malignant melanoma in particular should never be undertaken without previous histological proof that cancer is present. This is a rule that suffers only a few exceptions and if we do not follow it, sooner or later we will find that a major, and even a mutilating operation has been performed for a benign condition that clinically simulated cancer."

Apparently, there is a widespread belief that a malignant melanoma should never be biopsied because cutting into it or into its immediate vicinity might increase the incidence of lymphatic or hematogenous spread. The authors feel that there is no well-documented statistical proof that this danger exists.

T. J. C.

Primary Malignant Melanoma of the Oral Cavity. A Review of 105 Cases. A. P. Chaudhry, A. Hampel, and R. J. Gorlin. Cancer 11: 925, October, 1958.

"Primary malignant melanoma of the oral cavity is an extremely rare tumor, but it may not be as uncommon as the number of reported cases would indicate."

The site of predilection for malignant melanoma of the oral cavity in the upper jaw in particular is the hard palate.

Primary malignant melanoma of the oral cavity has a marked tendency for both regional and distant metastasis.

In the review of 105 cases, it was found that malignant melanoma occurs more often in men than in women; the average age of the patients was 50.5 years.

One case is reported in which the lesions were located on the upper right alveolar ridge and extended to the hard palate.

T. J. C.

ORAL MEDICINE

Hemifacial Spasm. M. L. Lewis. South. M. J. 50: 110, January, 1957.

Hemifacial spasm is an organic disease of the facial nerve, a distinct clinical entity to be differentiated from facial tics and other spasms of the head and neck. This condition is unusual but not rare.

The course of hemifacial spasm is in doubt, but it is believed to be a lesion of the lower motor neuron. There is twitching of the facial muscles, the eyelids are involved on the affected side, and spasm occurs during sleep.

The patient cannot control the spasms, and only muscles innervated by the facial nerve are affected.

Hemifacial spasm is a chronic progressive illness, with only rare spontaneous remissions.

Treatment has been fraught with poor results, temporary relief, facial paralysis, and disappointment.

T. J. C.

Nystatin in the Treatment of Candida Albicans Infections. E. S. Bereston. South. M. J. **50:** 547, April, 1957.

The treatment of all types of candida infection, until recently, consisted primarily of the use of gentian violet. Locally it was quite effective, but it discolored skin and clothing.

Nystatin, an antibiotic derived from *Streptomyces noursei,* is antifungal against *Candida albicans.* The drug can be given orally in a 500,000 unit tablet two to eight times a day, depending on the age and weight of the patient; it also can be administered as a powder dissolved in milk or as an ointment or lotion.

Effective and dramatic results were obtained in the treatment of thrush in infants.

T. J. C.

Bell's Palsy: A New Syndrome Associated With Treatment by Nicotinic Acid. C. E. Keme. A. M. A. Arch. Otolaryng. **68:** 28, July, 1958.

Bell's palsy (facial nerve paralysis) is a sympathetic paralysis, apparently caused by a vasoconstriction of the arterioles of the peripheral perineural vascular channels of the seventh nerve. Many patients give a history of exposure to cold or draft on the affected side of the face. When the diagnosis is established, treatment is started immediately. An initial dose of 100 to 150 mg. of nicotinic acid is given in the intramuscular injection and the reaction is observed. If the face or skin on the body shows marked flushing, then the correct maintenance dose has been found. In a series of seventy-four consecutive Bell's palsy cases which were treated by 100 to 250 mg. of nicotinic acid, excellent results were noted within two to four weeks.

T. J. C.

ORAL SURGERY

Treatment of Squamous Cell Carcinoma of the Tongue. H. W. Southwick, J. W. Otten, and D. P. Slaughter. Surgery **43:** 313, February, 1958.

SUMMARY

"1. In the treatment of cancer of the tongue, the primary tumor can be controlled essentially with equal effectiveness by surgery or by irradiation; for lesions at the base of the tongue irradiation is probably superior.

"2. Radical neck dissection is the treatment of choice for metastatic disease.

"3. Clinical evaluation of the neck for the presence of metastatic disease fails to detect its presence in at least forty per cent of the patients.

"4. Results are sufficiently improved when neck dissections are performed routinely as part of an en bloc procedure that serious consideration again should be given to elective neck dissection in conjunction with the primary treatment of carcinoma of the tongue."

T. J. C.